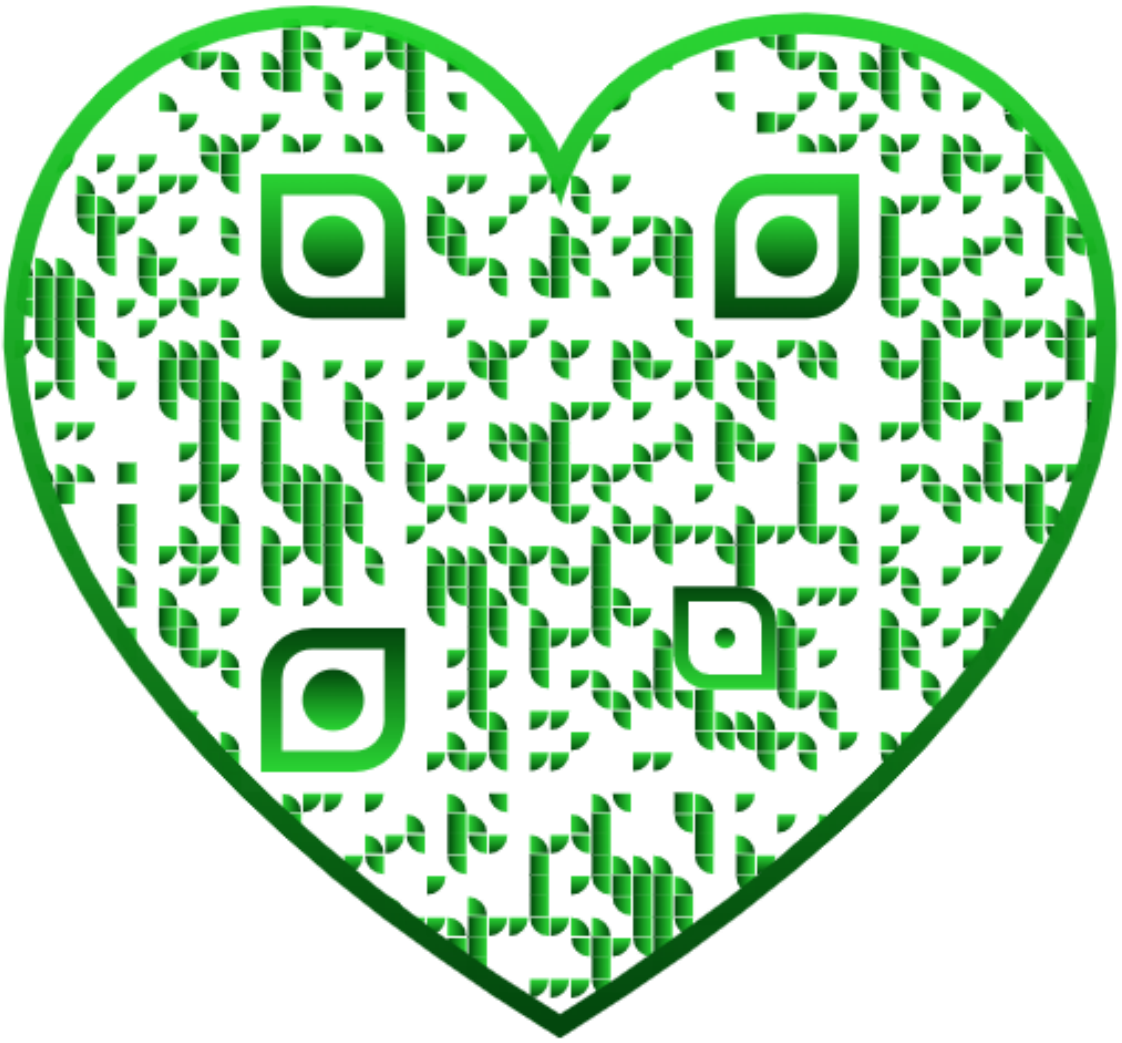
WHO consolidated guidelines on tuberculosis

Module 4: Treatment

Drug-susceptible tuberculosis treatment

World Health Organization



WHO consolidated guidelines on tuberculosis

Module 4: Treatment

Drug-susceptible tuberculosis treatment

World Health Organization

WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment.

ISBN 978-92-4-004812-6 (electronic version)

ISBN 978-92-4-004813-3 (print version)

© World Health Organization 2022

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; https://creativecommons.org/licenses/by-nc-sa/3.0/igo).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization (http://www.wipo.int/amc/en/mediation/rules/).

Suggested citation. WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

Sales, rights and licensing. To purchase WHO publications, see http://apps.who.int/bookorders. To submit requests for commercial use and queries on rights and licensing, see https://www.who.int/copyright.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Design by Inis Communication

Contents

Acknowledgements v

List of abbreviations vi

Definitions vii

Executive summary ix

Introduction 1

Objectives 3

Methods used to update the guidelines 5

- Scope of the guideline update 5
- Certainty of evidence and strength of recommendations 5
- Assessment of evidence and its grading 6
- External review 7
- Publication, dissemination, implementation, evaluation and expiry 7

Recommendations 9

- Treatment of drug-susceptible TB using 6-month regimen 9
- Treatment of drug-susceptible TB using 4-month regimens 16
- Drug-susceptible TB treatment and ART in people living with HIV 26
- The use of adjuvant steroids in the treatment of TB meningitis and pericarditis 28

Research priorities 31

References 33

Annex. Summary of changes in policy on DS-TB treatment since 2010 and mapping of recommendations in consolidated DS-TB guidelines 37

Web Annexes 53

Web Annex 1. Expert panels

Web Annex 2. Declarations of interest

Web Annex 3. PICO questions

Web Annex 4. GRADE evidence profiles and evidence-to-decision tables

Web Annex 5. 2010 and 2017 DS-TB Guidelines

https://apps.who.int/iris/bitstream/handle/10665/353398/9789240048140-eng.pdf

Acknowledgements

The production and writing of this document – WHO consolidated guidelines on tuberculosis. Module 4: Treatment: Drug-susceptible tuberculosis treatment – was coordinated by Fuad Mirzayev, with the support of Medea Gegia, Linh Nguyen and Kerri Viney, under the guidance of Matteo Zignol, and the overall direction of Tereza Kasaeva, Director of the WHO Global Tuberculosis Programme.

The World Health Organization (WHO) acknowledges and is grateful for the time and support of all individuals who have contributed to these efforts and gratefully acknowledges the contribution of all experts involved in the production of these guidelines.

The details on the participants and members of the Guideline Development Group and other groups and partners who contributed to the 2010, 2017 and 2022 guidelines update can be found in the Annexes.

This update was funded by grants provided to WHO by the United States Agency for International Development.

List of abbreviations

AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral treatment
CDC	United States Centers for Disease Control and Prevention
DST	Drug susceptibility testing
FDC	Fixed-dose combination
GDG	Guideline Development Group
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTB	Global TB Programme
HIV	Human immunodeficiency virus
MDR-TB	Multidrug-resistant tuberculosis
NGO	non-government organization
PICO	Population, Intervention, Comparator and Outcomes
TB	Tuberculosis
USAID	United States Agency for International Development
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

TB medicines

E	ethambutol
H	isoniazid
M or Mfx	moxifloxacin
Z	pyrazinamide
R	rifampicin
P or Rpt	rifapentine

Definitions

Drug-susceptible TB (DS-TB): A bacteriologically confirmed or clinically diagnosed case of TB without evidence of infection with strains resistant to rifampicin and isoniazid.

Drug susceptibility testing (DST): In vitro testing using either: 1) molecular, genotypic techniques to detect resistance-conferring mutations; or 2) phenotypic methods to determine susceptibility to a medicine.[1]

Extensive (or advanced) pulmonary tuberculosis (TB) disease: Presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged under 15 years, advanced disease is usually defined by the presence of cavities or bilateral disease on chest radiography.[2]

New case: a newly registered episode of TB in a patient who has never been treated for TB or who has taken anti-TB medicines for less than 1 month.

Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB): TB caused by *M. tuberculosis* strains resistant to isoniazid and susceptible to rifampicin.

A **bacteriologically confirmed TB** case is one from whom a biological specimen is positive by smear microscopy, culture or a WHO-recommended rapid diagnostic (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.

A **clinically diagnosed TB** case is a person who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation.

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree.

Extrapulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges).

Rifampicin-resistant TB (RR-TB): TB caused by *M. tuberculosis* strains resistant to rifampicin. These strains may be susceptible or resistant to isoniazid (i.e. MDR-TB), or resistant to other first-line or second-line TB medicines. In these guidelines and elsewhere, MDR-TB and RR-TB cases are often grouped together as MDR/RR-TB and are eligible for treatment with MDR-TB regimens.

---

[1] Implementing tuberculosis diagnostics: a policy framework. Geneva: World Health Organization; 2015. (http://apps.who.int/iris/bitstream/10665/162712/1/9789241508612_eng.pdf, accessed 27 September 2021).

[2] WHO consolidated guidelines on tuberculosis. Module 4: treatment – drug-resistant tuberculosis treatment. (https://apps.who.int/iris/rest/bitstreams/1280998/retrieve, accessed 27 September 2021).

Pre-XDR-TB:[3] TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone.[4]

XDR-TB: TB caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) strains that fulfil the definition of MDR/RR-TB and that are also resistant to any fluoroquinolone and at least one additional Group A drug.[5]

Treatment support terminology in this document is used to describe an approach to supporting patients who are taking prescribed doses of TB medicines in order to help ensure adherence to treatment and maximize its efficacy. Treatment support needs to be provided in the context of people-centred care and should be based on the individual patient's needs, acceptability and preferences. It includes aspects of support, motivation and understanding of patients without coercion. Historically, this group of interventions were labelled as "directly observed treatment" or DOT.

[3] Meeting report of the WHO expert consultation on the definition of extensively drug-resistant tuberculosis, 27–29 October 2020. Geneva: World Health Organization; 2021. (https://www.who.int/publications/i/item/meeting-report-of-the-who-expert-consultation-on-the-definition-of-extensively-drug-resistant-tuberculosis, accessed 27 September 2021).

[4] The fluoroquinolones include levofloxacin and moxifloxacin because these are the fluoroquinolones currently recommended by WHO for inclusion in shorter and longer regimens.

[5] The Group A drugs are currently levofloxacin or moxifloxacin, bedaquiline and linezolid; therefore, XDR-TB is MDR/RR-TB that is resistant to a fluoroquinolone and either bedaquiline or linezolid (or both). The Group A drugs may change in the future. Consequently, the terminology "Group A" is appropriate here and will apply to any Group A drugs in the future.

Executive summary

Tuberculosis (TB) affects an estimated 10 million people per year (range 8.9–11.0 million) and is one of the world's leading infectious disease killers. TB is responsible for an estimated 1.2 million TB deaths among HIV-negative people (range, 1.1–1.3 million), and an additional 208 000 deaths among HIV-positive persons (range, 177 000–242 000). Of the estimated 10 million, approximately 70% are diagnosed and treated and also reported to the World Health Organization (WHO), resulting in 7.1 million TB notifications by National TB Programmes. Of the 7.1 million persons notified in 2019, 5.9 million (84%) had pulmonary TB *[1]*.

For several decades WHO has developed and issued recommendations on the treatment of TB. The most recent WHO recommendations for treating people suffering from drug-susceptible TB have been defined in WHO's *Guidelines for treatment of drug-susceptible tuberculosis and patient care*, 2010 and 2017 updates (see Annex). A focus of these guidelines was a 6-month treatment regimen composed of four first-line TB medicines, namely isoniazid, rifampicin, ethambutol and pyrazinamide, recommended for treatment of drug-susceptible TB. This regimen is well known and has been widely adopted worldwide for decades; while using it, approximately 85% of patients will have a successful treatment outcome. This regimen is based on seminal TB treatment studies conducted by the British Medical Research Council in the second half of 20th century. In addition to the recommendation on the treatment regimen, the 2010 and 2017 updates of the guideline included a number of recommendations on the modalities and formulations used for treatment, frequency of treatment administration, special situations and patient care during treatment. The consolidated and updated guidelines in the current *Module 4: Treatment – Drug-susceptible tuberculosis treatment* brings together, without modifications, all valid and evidence-based recommendations from the 2010 and 2017 guideline updates and adds a new section stemming from the most recent round of guidelines development in 2021 – the recommendations for the 4-month regimens to treat drug-susceptible TB (DS-TB).

This module of the consolidated guidelines includes only recommendations related to treatment since all recommendations on patient care and support, for both the drug-susceptible and drug-resistant TB (DR-TB) have been merged in a dedicated guideline module on "*Tuberculosis care and support*".

The update of the guidelines for treatment of DS-TB is important in the context of the End TB Strategy *[2]*, which recommends treatment and patient support for all people with TB. This update by WHO aims to use the best available evidence on the treatment of DS-TB in order to inform policy decisions made by national TB control programme managers, national policy-makers and medical practitioners in a variety of geographical, economic and social settings.

The objectives of the updated *Guidelines* are:

1) to provide updated recommendations based on newly emerged evidence on the treatment of drug-susceptible TB; and

2) to provide a summary of changes in the new guidelines together with all the existing and valid WHO recommendations on the treatment of DS-TB.

The guidance provided in this module outlines specific WHO recommendations on the overall treatment management, care and monitoring of patients with DS-TB. It brings forward recommendations developed by various WHO-convened guideline development groups (GDGs), using the Grading of

Recommendations Assessment, Development and Evaluation (GRADE) approach to summarize the evidence, and to formulate policy recommendations and accompanying remarks. The recommendations and remarks in the current module on the treatment of DS-TB are the result of collaborative efforts of professionals from a range of specialties who have extensive expertise and experience in public health policy, TB programme management, the care and management of patients with TB, members of affected communities and TB survivors.

The recommendations included herein are part of WHO's consolidated guidelines on TB and are primarily intended for use by national TB control programmes, public health agencies, and other key constituencies involved in the planning, implementation and monitoring of activities for the programmatic management of DS-TB.

These recommendations have been developed through several meetings of the GDGs and have then been consolidated in the present module. The recommendation on the use of the 4-month regimens stem from the GDG meetings that took place in 2021. The remainder of the recommendations have been consolidated from the GDGs that took place in 2009 and 2016, as expressed in the 2010 and 2017 guidelines update.

Summary of WHO recommendations on drug-susceptible TB treatment

Treatment of drug-susceptible TB using 6-month regimen

1. ***New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR (strong recommendation, high certainty of evidence).***
2. ***Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy (strong recommendation, high certainty of evidence).***
3. ***In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency (conditional recommendation, very low certainty of evidence).***
4. ***The use of fixed-dose combination (FDC) tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB (conditional recommendation, low certainty of evidence).***
5. ***In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended (strong recommendation, high certainty of evidence).***

Treatment of drug-susceptible TB using 4-month regimens

6. ***People aged 12 years or older with drug-susceptible pulmonary TB may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide (2HPMZ/2HPM) (conditional recommendation, moderate certainty of evidence) – new recommendation.***
7. ***In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used (strong recommendation, moderate certainty of evidence) – new recommendation.***

Drug-susceptible TB treatment and antiretroviral therapy (ART) in people living with HIV

8. *It is recommended that TB patients who are living with HIV should receive at least the same duration of TB treatment as HIV-negative TB patients (strong recommendation, high certainty of evidence).*

9. *ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV. Adults and adolescents (strong recommendation, low to moderate certainty of evidence); Children and infants (strong recommendation, very low certainty of evidence).*

The use of adjuvant steroids in the treatment of TB meningitis and pericarditis

10. *In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used (strong recommendation, moderate certainty of evidence).*

11. *In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used (conditional recommendation, very low certainty of evidence).*

Introduction

For several decades the World Health Organization (WHO) developed and issued recommendations on the treatment of TB. The most recent WHO recommendations for treating people suffering from drug-susceptible TB (DS-TB) have been defined in the WHO's *Guidelines for treatment of drug-susceptible tuberculosis and patient care*, 2010 and 2017 updates *[3, 4]*. These guidelines focused on the 6-month treatment regimen composed of four first-line TB medicines, namely isoniazid, rifampicin, ethambutol and pyrazinamide, recommended for treatment of DS-TB. This regimen is well known and has been widely adopted worldwide for decades; while using it, approximately 85% of patients will have a successful treatment outcome. This regimen is based on seminal TB treatment studies conducted by the British Medical Research Council in the second half of 20th century *[5]*. In addition to the recommendation on the treatment regimen, the 2010 and 2017 guideline updates included a number of recommendations on the modalities and formulations used for treatment, frequency of treatment administration, special situations and patient care during treatment. The consolidated and updated guidelines in the current *Module 4: Treatment – Drug-susceptible tuberculosis treatment*, brings together, without modifications, all valid and evidence-based recommendations from the 2010 and 2017 guidelines and adds a new section based on the most recent round of guidelines development – the recommendations for the 4-month treatments of DS-TB.

This module of the consolidated guidelines includes recommendations related to treatment of DS-TB in all age groups. All recommendations on patient care and support during treatment, for both the DS-TB and drug-resistant TB (DR-TB) have been merged in a dedicated module on "*Tuberculosis care and support*". The recommendations specific for children and adolescents are consolidated in the module on *Management of tuberculosis in children and adolescents*.

The update of the guidelines for treatment of DS-TB is important in the context of the End TB Strategy *(1)* which recommends treatment and patient support for all people with TB.

Objectives

The present guideline update aims to use the best available evidence on the treatment of DS-TB in order to inform policy decisions made in this technical area by national TB control programme managers, national policy-makers and medical practitioners in a variety of geographical, economic and social settings.

The objectives of the updated *Guidelines* are:

1) to provide updated recommendations based on newly emerged evidence on the treatment of drug-susceptible TB; and

2) to provide a summary of changes in the new guidelines together with all existing and valid WHO recommendations on the treatment of DS-TB.

Methods used to update the guidelines

Scope of the guideline update

The scope of the 2021 update of the DS-TB treatment guideline was to consolidate in one document all the previous evidence-based policy recommendations on treatment of DS-TB (previously presented in two separate guideline documents) and to add new recommendations. Thus the current module brings together all recommendations that are valid from previous guidelines without any modifications as no additional reviews have been performed. In addition to these previous valid recommendations, the 2021 update presents new recommendations on the 4-month regimens emerging from the Guideline Development Group (GDG) meetings in 2021. Now that the guidelines are consolidated, WHO will strive to review and update individual recommendations based on the emerging evidence.

Certainty of evidence and strength of recommendations

The recommendations in these guidelines qualify both their strength and in the certainty of the evidence on which they are based. The certainty of the evidence is categorized into four levels (Table 1). The criteria used by the evidence reviewers to qualify the certainty of evidence are summarized in the GRADE tables (see Web Annex 4). Several factors may increase or decrease the certainty of evidence (see tables 12.2b and 12.2c in the *WHO handbook for guideline development [6]*. The highest certainty rating is usually assigned to evidence from randomized controlled trials, while evidence from observational studies is usually assigned a low or very low certainty value at the start.

A recommendation may be strong or conditional. Apart from the certainty of evidence, the strength of a recommendation is determined by the balance between desirable and undesirable effects, values and preferences, and costs or resource allocation. For strong recommendations, the GDG is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects. For conditional recommendations, the GDG considers that the desirable effects probably outweigh the undesirable effects. The strength of a recommendation has different implications for the individuals affected by these guidelines (Table 2).

Table 1. Certainty in the evidence

Certainty in the evidence	Definition
High (⊕⊕⊕⊕)	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate (⊕⊕⊕◯)	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low (⊕⊕◯◯)	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low (⊕◯◯◯)	Any estimate of effect is very uncertain.

The text of the recommendation itself should be read along with the accompanying remarks which summarize: 1) the evidence on which the recommendation was made; 2) the anticipated desirable and undesirable effects of the interventions in assessing the balance of expected benefits to risks; and 3) other considerations which are important to the implementation of the policy.

Assessment of evidence and its grading

The development of these guidelines required a substantial evidence review and assessment using the GRADE process, as stipulated by WHO's Guidelines Review Committee *[7]*. The systematic reviews focused primarily on the randomized controlled trials with direct comparison between the intervention and comparator. However, data on the outcomes from the observational cohort studies were also summarized and assessed by the GDGs, especially when limited or no evidence from randomized controlled trials was available.

Table 2. Implications of the strength of a recommendation for different users

Perspective	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guidelines could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients, and that patients must be helped to arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
For policy-makers	The recommendation can be adopted as policy in most situations.	Policy-making will require substantial debate and the involvement of various stakeholders.

Source: Adapted from Guyatt et al. *[8]*

The GDG membership represented a broad cross-section of experts, future users of the guidelines as well as affected persons. All decisions about the recommendations were reached by discussion and consensus, including on the strength of the recommendations and, where appropriate, the conditions to be attached to the recommendations. The GDG chairs facilitated the discussions in order to reach consensus during the meetings.

External review

The process of peer review involved an External Review Group which was composed of experts and end-users from national programmes, technical agencies and WHO regional offices. These persons provided their reviews and inputs on the completed draft guidelines after all comments by GDG members were incorporated.

Publication, dissemination, implementation, evaluation and expiry

These guidelines are published on the website of WHO's Global TB Programme (WHO/GTB)[6] and can be freely downloaded (in pdf and other electronic formats). It is also expected that the evidence reviews and recommendations will be published in peer-reviewed journals to improve dissemination of the main messages. The updates to policy guidance are also reflected in the implementation guidance on TB management and the revision of the *WHO operational handbook on tuberculosis – Module 4: Treatment*.

Following consolidation of the guidelines, WHO will strive to review and update individual recommendations based on the emerging evidence.

WHO works closely with its regional and country offices, as well as with technical and funding agencies and partners, to ensure wide communication of the updated guidance in technical meetings and training activities. WHO collaborates with technical partners at different levels to support national TB programmes in adopting new recommendations in their national TB policies and guidelines.

[6] See: https://www.who.int/health-topics/tuberculosis

Recommendations

Treatment of drug-susceptible TB using 6-month regimen

Recommendation 1.

New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR (strong recommendation, high certainty of evidence)

Remarks

A: The recommendation also applies to extrapulmonary TB – except TB of the central nervous system, bone or joint for which some expert groups suggest longer therapy.

B: WHO recommends that national TB control programmes provide supervision and support for all TB patients in order to ensure completion of the full course of therapy.

C: WHO recommends drug resistance surveys (or surveillance) for monitoring the impact of the treatment programme, as well as for designing standard regimens.

Source of recommendation

This recommendation was first put forward in 2010 and was considered valid in 2017 guidelines update (see mapping of recommendations in Annex). The recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

Justification and evidence

A systematic review and meta-analysis included 21 472 participants in 312 arms of 57 randomized controlled trials conducted in various regions of the world since 1965 *[9]*. In three of the 57 trials, patients were randomly assigned to either a 2-month rifampicin or a 6-month rifampicin arm; rates of failure, relapse and acquired drug resistance were compared "head-to-head" across the two study arms. In a multivariate regression analysis, each arm of the 57 trials was treated as a separate cohort and results were adjusted for potentially confounding patient and treatment factors.

The three studies with head-to-head comparisons showed that the risk of relapse after a 6-month rifampicin regimen was significantly lower than that after a 2-month rifampicin regimen. If a country were to change from a 2-month to a 6-month rifampicin regimen, the benefit would be an estimated 112 relapses averted per 1000 TB patients.

Regression analysis suggests that changing to a 6-month regimen would significantly reduce failure and acquired drug resistance rates, in addition to relapse rates.[7] This analysis found that regimens with 5–7 months of rifampicin have 0.43 times the failure rate, and 0.32 times the relapse rate of regimens with 1–2 months of rifampicin. Among the failures and relapses from regimens with 5–7 months of rifampicin, the rate of acquired drug resistance is 0.28 times that of the regimens with 1–2 months of rifampicin.

Patients with isoniazid resistance would realize major benefits if the 2-month rifampicin regimen were replaced with a 6-month regimen. Among patients with isoniazid mono-resistance at the start of treatment, 38% relapsed after treatment with 2-month rifampicin regimens, which is significantly higher than the 5.5% relapse rate after treatment with 6-month rifampicin regimens. Thus, changing to the 6-month rifampicin regimen would avert 325 relapses per 1000 patients who start treatment with isoniazid resistance.

Even for patients with pan-susceptible TB, the proportion who relapsed after the 2-month rifampicin regimen was 8.2%, which was significantly higher than the 3.1% for the 6-month rifampicin regimen.

When the first course of therapy is considered along with retreatment for patients who fail or relapse, it is estimated that the 6-month rifampicin regimen would avert between 3 and 12 deaths per 1000 compared with the 2-month rifampicin regimen across 7 countries modelled with a range of drug resistance among new patients. In addition, 0.6–4.4 failures and relapses with drug resistance other than MDR-TB would be averted per 1000 TB patients, but an additional 0.6–1.3 MDR-TB cases would be generated.

Among patients who failed or relapsed after their first course of treatment containing 6 months of rifampicin, regression analysis found a reduction in overall acquired drug resistance; however, the pattern of acquired drug resistance was different from that in patients who received the 2-month rifampicin regimen. The risk of acquiring drug resistance other than MDR-TB is higher with the 2-month rifampicin regimen, but the risk of acquiring MDR-TB is higher with the 6-month rifampicin regimen. Among failures, the proportion with MDR-TB is predicted to be 4–56% after initial treatment with the 2-month rifampicin regimen but 50–94% after initial treatment with the regimen containing 6 months of rifampicin.

Subgroup considerations

The interactions of rifampicin with antiretroviral therapy (ART) are of concern. Switching to the 6-month rifampicin regimen means that these drug interactions must be taken into account for the full 6 months rather than for just the first 2 months of therapy. However, the 6-month rifampicin regimen has marked benefits for persons living with HIV, and the drug interactions can be managed *[10]*.

Implementation considerations

To help minimize the acquisition of MDR-TB, it is critically important that national TB control programmes ensure adequate supervision of rifampicin. Implementing patient supervision for the 4-month continuation phase will require additional resources in areas where the continuation phase has been self-administered – an investment that may be offset by the savings from relapses (and therefore retreatments) averted. In 2008, 23 countries (including four that are considered high-burden) still used the 2-month rifampicin regimen for their new patients. These countries reported 706 905 new cases in 2007, or 13% of the global new TB notifications that year.

[7] The difference in failure and acquired drug resistance was not statistically significant in these three randomized controlled trials.

Monitoring and evaluation

This recommendation places high value on saving lives. Given both the high certainty of evidence for this benefit and the fact that the potential harm of acquired DR-TB can be mitigated by supervision of treatment. Periodic drug resistance surveys (or ongoing surveillance) in each country are essential for monitoring the impact of the regimen and the overall treatment programme.

Recommendation 2.

Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy (strong recommendation, high certainty of evidence)

Source of recommendation

This recommendation was first put forward in 2010 and considered valid in the 2017 guidelines update (see mapping of recommendations in Annex). The recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

Justification and evidence

A systematic review and meta-analysis included 21 472 participants in 312 arms of 57 randomized controlled trials conducted in various regions of the world since 1965 *[9]*. In a multivariate regression analysis, each arm of the 57 randomized controlled trials was treated as a separate cohort, and results were adjusted for potentially confounding patient and treatment factors. Only one study of 223 patients evaluated a rifampicin-containing regimen administered twice weekly throughout therapy; this study was not included in the meta-analyses.

No significant increase in failure, relapse or acquired drug resistance was found when daily dosing throughout therapy was compared with the following intermittent regimens in new TB patients overall, namely: daily then thrice weekly; daily then twice weekly; or thrice weekly throughout therapy.

However, the regression analysis showed that patients being treated thrice weekly throughout therapy had rates of acquired drug resistance that were 3.3 times higher than those in patients who received daily drug administration throughout treatment.

The meta-analysis revealed no difference in rates of failure, relapse or acquired drug resistance in pan-susceptible new patients being treated with these dosing schedules. However, the use of a three times weekly intensive phase schedule in patients with pre-treatment isoniazid resistance was associated in another meta-analysis with a significantly higher risk of failure and acquired drug resistance *[11]*.

Implementation considerations

When based in a health facility, daily administration of therapy places a larger burden on TB programmes and patients than does intermittent therapy. Intermittent regimens require stronger programmes with higher-quality patient supervision, but all regimens should be provided with full patient supervision and support.

Studies of patients' preferences for dosing schedules were not systematically reviewed. The higher isoniazid dose used in intermittent therapy was not considered to have an increased incidence of adverse effects. The rifampicin dosage was unchanged when using intermittent therapy.

In an international, multicentre, randomized trial (Union Study A), Jindani, Nunn & Enarson found thrice weekly dosing resulted in significantly lower culture conversion rates at 2 months [12]. In developing recommendations, this endpoint was ranked by the GDG as important but not critical for decision-making and was not part of the systematic review.

For new patients without HIV infection, high- certainty of evidence demonstrated no significant difference between regimens that were administered daily throughout treatment, daily initially and then intermittently in the continuation phase, or thrice weekly throughout treatment.

Daily dosing is optimal because it probably achieves better adherence under programme conditions. While the definition of the term varies across countries, "daily" is considered to mean at least five times per week. In addition, meta-analyses showed the superiority of daily (compared with thrice weekly) intensive-phase dosing for patients with pre-treatment isoniazid resistance and for preventing acquired drug resistance in patients overall.

Recommendation 3.

In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy and daily dosing remains the recommended dosing frequency (conditional recommendation, very low certainty of evidence).

Source of recommendation

This recommendation was first put forward in 2010 and then updated in the 2017 guidelines (see mapping of recommendations in Annex). It is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

Justification and evidence

The use of intermittent dosing of TB medications has been adopted in some geographical settings in an effort to improve treatment adherence and to reduce the burden on the health-care system due to daily treatment support. However, it was unclear how this intermittent dosing might affect treatment outcomes. In addition to the evidence from a systematic review conducted in 2009 of treatment regimens with intermittent dosing schedules *[9]*, this systematic review was updated with the most recent randomized controlled trials *[13–18]*.

Evidence showed that when thrice-weekly dosing throughout therapy was compared to daily dosing throughout therapy, patients who received thrice-weekly dosing had a higher risk of treatment failure, disease relapse and acquired drug resistance in both drug-susceptible disease and when the strain susceptibility was unknown. Consequently, thrice-weekly dosing in the intensive phase should never be used.

Likewise, when thrice-weekly dosing during the continuation phase only is compared to daily dosing throughout, there were higher rates of treatment failure and relapse in the patients that received thrice-weekly treatment during the continuation phase. In this case, acquired drug resistance rates did not differ. If thrice-weekly dosing during the continuation phase is used, it is essential to make sure that patients do not miss any dose of the medications and that treatment support is used.

In this review, the use of twice-weekly dosing in the continuation phase only was also reviewed. Twice-weekly dosing in the continuation phase only had higher rates of treatment failure, disease relapse

and drug resistance than thrice-weekly dosing in the continuation phase only. As a result, twice-weekly dosing should never be used during any part of TB therapy.

Adherence to treatment was not adequately addressed in the reviewed studies to be included as an outcome. However, in most studies included in the systematic review, intermittent dosing used treatment support, while the use of treatment support during daily dosing was variable.

The GDG also considered that health equity would be adversely affected with intermittent dosing because more vulnerable populations would receive inferior treatment if intermittent dosing were used. This is because people living in more resource-constrained settings would be at greater risk of missing doses of medication, not only because of their difficulty in reaching a clinic but also because of the risk of medication stock-outs in clinics. Additionally, patients who are co-infected with HIV or have other comorbidities may not absorb TB medications well and therefore they may receive less medication than they are ingesting. In order for TB medication to be used as part of a treatment regimen, no doses may be missed with thrice-weekly intermittent dosing during the continuation phase because the rates of unfavourable outcomes may rise. Consequently, populations that are more vulnerable are at risk of missing doses of medication or of not absorbing the doses well, and intermittent dosing puts them in a situation where there is an increased risk of unfavourable outcomes.

Intermittent dosing may also create problems at national and international levels by resulting in requirements for different drug manufacturing and packaging and a reduced drug supply buffer, leading to an increased risk of TB medication stock-outs.

Given the findings in this review, all countries are encouraged to use daily dosing exclusively in both the intensive and the continuation phases of treatment. Although two separate evidence assessments were conducted on thrice-weekly dosing in the intensive phase and the continuation phase, both the formulated recommendations were conditional and there was very low certainty in the evidence. A combined recommendation for both intensive and continuation phases was formulated to make it more convenient for use by the end-users.

Subgroup considerations

This recommendation is the same for HIV-negative people and for people living with HIV.

The data used in this review examined only patients with drug-susceptible pulmonary TB who had no extenuating circumstances – such as adverse reactions which might require modification of the dosing schedule.

Children were not considered specifically in this review. However, there is no biologically plausible reason why this recommendation should not also apply to children. It is recommended that all children receive daily dosing of TB medications during the intensive and continuation phases of therapy for the same reason as adults. See WHO's 2014 guideline *Guidance for national tuberculosis programmes on the management of tuberculosis in children [19]* for recommendations on the daily dosing of children with DS-TB.

Implementation considerations

There are no new implementation considerations as the recommended daily treatment is already widespread practice. However, intermittent dosing is still used in some countries. In such exceptional cases, implementation of the recommendation to use exclusively daily dosing in the intensive and continuation phases of TB therapy is likely to have implications for medication procurement, practitioner training, change of programme practice and patient support.

Monitoring and evaluation

There are no new monitoring and evaluation recommendations as the standard of care (daily dosing of medications during the intensive and continuation phases of therapy) is being recommended.

Recommendation 4.

The use of fixed-dose combination tablets is recommended over separate drug formulations in treatment of patients with drug-susceptible TB (conditional recommendation, low certainty of evidence)

Source of recommendation

This recommendation was first put forward in the 2017 guidelines update (see mapping of recommendations in Annex). It is copied without modification into this consolidated document and appears exactly as in the 2017 guidelines.

Justification and evidence

The evidence presented to the GDG was based on a systematic review of randomized controlled trials done by Albanna et al. *[20]* and by a recent Cochrane review *[21]*. This evidence showed that the fixed-dose combination (FDC) tablets are non-inferior and equally effective as separate drug formulations in terms of treatment failure, death, treatment adherence and adverse events. There was a small increase in 2-month culture conversion with FDC treatment; however, there was no difference in culture conversion rates by the end of treatment. Patient satisfaction was higher among persons treated with FDCs. A slightly higher rate of disease relapse and acquired drug resistance among patients treated with FDCs compared with those treated with separate drug formulations was not statistically significant.

Patient treatment satisfaction with FDCs was considered the most important factor for making decisions on this recommendation.

Studies in these reviews did not evaluate bioavailability of the drugs in the FDCs, but previous studies did not indicate that the FDC formulations used had significant bioavailability issues *[20]*. As no pharmacokinetic studies were done on these FDC formulations, the bioavailability of drugs within the FDCs versus the separate drug formulations remains an important consideration that indicates the need to procure FDCs of demonstrated bioavailability *[22–24]*. This area requires further research.

FDCs may provide programme benefits by making the ordering of medication easier, simplifying supply chain management, reducing the occurrence of stock-outs, and facilitating drug delivery and prescription preparation. FDCs may also provide benefits – especially in settings with a large number of TB patients and a limited number of health-care workers – by reducing the need for additional health-care staff and training in the dosing and dispensing of medications, as well as by contributing to a lower pill burden for patients. Nevertheless, national TB programmes are advised to have a quantity of separate drug formulations available for certain treatment conditions. Having single drug formulations available would be beneficial to national TB programmes when designing MDR-TB regimens that include some first-line drugs (i.e. pyrazinamide, EMB, high-dose isoniazid), when providing preventive therapy, and in cases of adverse reactions to TB medications when drugs must be reintroduced one at a time.

The GDG acknowledged that greater patient satisfaction is an advantage of FDCs over separate drug formulations.

Subgroup considerations

The reduced pill burden as a result of using FDCs may be especially valuable in patients with co-morbidities (notably HIV infection) and paediatric patients (who may have some difficulty in swallowing large amounts of medications).

Patients with some specific medical conditions (e.g. intolerance to certain TB drugs, liver or renal function impairment) are likely to require individual medication dose adjustment which can be done only with separate drug formulations.

Implementation considerations

There are no specific implementation considerations as the use of FDC formulations is already widespread.

Monitoring and evaluation

There are no specific new recommendations for monitoring and evaluation as the use of both types of drug formulation is already widespread.

Recommendation 5.

In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, the extension of the intensive phase is not recommended (strong recommendation, high certainty of evidence)

Source of recommendation

This recommendation was first put forward in 2010 and considered valid in the 2017 guidelines update (see mapping of recommendations in Annex). It is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

Justification and evidence

The systematic review identified only one relevant study (with results published in 2012). A study still under way (at moment of review) in Bangladesh of a 6-month rifampicin-containing regimen randomized 3775 new smear-positive patients who remained positive at 2 months to either the 1-month extension arm (extension of the intensive phase by 1 month) or the no-extension arm *[25]*.

Preliminary results at 1 year of follow-up showed that patients in the 1-month extension arm had a significantly lower relapse rate (relative risk 0.37, 95% CI 0.21, 0.66) than patients in the no-extension arm. A smaller decrease in failure in the 1-month extension arm was not statistically significant. Given the preliminary nature of the results and the passive follow-up of patients, the evidence from the Bangladesh study was graded with moderate certainty.

In 1000 TB patients with a 7% risk of relapse, the Bangladesh study predicts that extending the treatment of 183 patients who are smear-positive at 2 months would avert 16 of the 70 expected

relapses. However, to achieve this 23% reduction in relapses, 158 patients per 1000 would be incorrectly predicted to relapse; consequently their treatment would be extended unnecessarily.

While extending rifampicin beyond 6 months reduces the risk of relapse, there is insufficient evidence to determine which patients are most likely to benefit. Historically, when the new patient regimen included only 2 months of rifampicin, the extension of the intensive phase meant an extra month of supervised rifampicin. This extra month is less important now as the current recommended regimen is 6 months of supervised rifampicin. Given these considerations, together with preliminary results from one moderate-certainty study that showed only modest benefit, a conditional recommendation was made not to extend treatment on the basis of a positive smear at 2 months.

Treatment of drug-susceptible TB using 4-month regimens

Recommendation 6.

People aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide[8] (conditional recommendation, moderate certainty of evidence) – new recommendation.

Source of recommendation

This recommendation was developed following the advice of the GDG convened in April 2021 to review data from a randomized controlled trial that assessed the safety and effectiveness of 4-month regimens for the treatment of DS-TB.

Justification and evidence

Since 2010, the WHO guidelines have recommended treating persons with DS-TB with a 6-month regimen composed of four first line TB medicines – isoniazid, rifampicin, ethambutol and pyrazinamide – where rifampicin is used for 6 months (2HRZE/4HR)*[4]*. This regimen is based on seminal TB treatment studies conducted by the British Medical Research Council in the 1980s *[5]* and has been widely adopted worldwide. Using it, approximately 85% of patients will have a successful treatment outcome *[1]*. Despite its familiarity, safety and efficacy, many patients find the 6-month regimen difficult to complete due to its length. In fact, long treatment regimens present serious challenges both to patients and to the programmatic management of TB globally.

Since the discovery of first-line anti-TB medicines and treatment regimens, there has been a search for shorter and more effective treatments for TB disease. This has resulted in various trials and other studies designed to assess whether treatment can be shortened, while remaining highly effective. Three phase III trials (i.e. REMoxTB, OFLOTUB, RIFAQUIN) failed to demonstrate non-inferiority of shorter regimens to treat DS-TB *[13, 14, 26]*. A recent phase III trial (TBTC study 31/ACTG A5349, or S31/A5349, referred to below as "Study 31") assessed the safety and efficacy of two 4-month regimens for the treatment of DS-TB *[27]*. Study 31was the first and only phase III trial to demonstrate the non-inferiority of the 4-month regimen for treatment of DS-TB when compared to the standard of care. The

[8] Two months of isoniazid, rifapentine, moxifloxacin, and pyrazinamide, followed by two months of isoniazid, rifapentine, and moxifloxacin

dedicated Cochrane review[9] in 2019 and the literature search for the period 2019–2021 performed prior to the GDG failed to identify any studies other than Study 31; therefore this was the only trial to provide evidence for this GDG review.

Study 31 was an international, multicentre, randomized, open-label, controlled, three-arm non-inferiority trial among adolescents and adults (aged 12 years and above) with smear-positive[10] and culture-positive pulmonary DS-TB *[27]*. Study participants were recruited from 13 countries. The study objectives were to evaluate the efficacy of: 1) a rifapentine-containing regimen to determine whether the single substitution of rifapentine for rifampicin makes it possible to reduce the duration of treatment for drug-susceptible pulmonary TB to four months; and 2) a rifapentine-containing regimen that additionally substitutes moxifloxacin for ethambutol and continues moxifloxacin throughout treatment, to determine whether the duration of treatment can be reduced, compared with the currently recommended 6-month regimen using a non-inferiority margin of 6.6 percentage points *[27]*.

The rifapentine-moxifloxacin arm was the only arm to demonstrate non-inferiority when compared to the standard of care (the WHO recommended regimen of six months of treatment with rifampicin, isoniazid, pyrazinamide and ethambutol) and thus the regimen was the one reviewed by the GDG. This regimen consisted of eight weeks of daily isoniazid (H), rifapentine (P), moxifloxacin (M) and pyrazinamide (Z) , followed by nine weeks of daily isoniazid, rifapentine, and moxifloxacin (2HPMZ/2HPM). The dose of rifapentine used was 1200 mg daily. The primary efficacy end point of Study 31 was TB disease-free survival at 12 months after randomization, while the primary safety end point was the proportion of participants with grade 3 or higher adverse events during the study drug treatment.

In the trial, a total of 2 516 patients from 34 sites (in Brazil, China, Haiti, India, Kenya, Malawi, Peru, South Africa, Thailand, Uganda, USA, Viet Nam and Zimbabwe) were randomly assigned to a treatment group. The microbiologically eligible population[11] included 791 patients with TB in the rifapentine-moxifloxacin arm and 768 in the standard of care control arm. The GDG accepted the outcomes used by the Study 31 for analysis, using the microbiologically eligible population as defined by the study to minimize bias, and using the safety analysis population (as defined by the study protocol) for the review of all-cause mortality and adverse events. The proportion of patients who were cured[12] was similar in both arms (84.5% in the rifapentine-moxifloxacin arm versus 85.4% for the standard of care, relative risk (RR) 0.99, 95% CI: 0.95–1.03). Retention on treatment was high for both arms, namely: 99.7% for the rifapentine-moxifloxacin arm and 99.0% for the standard of care arm (RR: 1.01, 95% CI: 1.00–1.02). All-cause mortality recorded within 14 days after the end of treatment was reported for 0.4% of patients in the rifapentine-moxifloxacin arm versus 0.8% in the standard of care (RR 0.42, 95% CI: 0.11–1.61); and grade 3 or higher adverse events were noted in 18.8% of participants in the rifapentine-moxifloxacin arm versus 19.3% in the standard of care arm (RR 0.97, 95% CI: 0.76–1.24). There were no statistically significant differences in the proportion of patients who were cured when comparing the rifapentine-moxifloxacin arm to the standard of care arm for all four subgroups that were analysed (persons living with HIV infection; persons with extensive disease, based on extent of disease on chest radiography, persons with diabetes mellitus; and persons with a low body weight, less than 17.9 kg/m3). There was little or no difference in all-cause mortality and adverse events during treatment – a slight increase in retention on treatment was noted in the rifapentine-moxifloxacin arm (RR 1.01, 95% CI: 1–1.02) and the evidence was uncertain with regard to acquisition of drug resistance.

---

[9] Grace AG, Mittal A, Jain S, Tripathy JP, Satyanarayana S, Tharyan P at al. Shortened treatment regimens versus the standard regimen for drug-sensitive pulmonary tuberculosis. Cochrane Database Syst Rev. 2019;(12):CD012918. doi: 10.1002/14651858.CD012918.pub2

[10] Smear positive for acid-fast bacilli on smear microscopy or smear positive for M. tuberculosis by GeneXpert MTB/RIF® ("Xpert", Cepheid Inc., Sunnyvale, CA) testing with semi-quantitative result of "medium" or "high".

[11] The microbiologically eligible population excludes persons with resistance to the medicines used for treatment; those with no baseline positive TB culture and others that were not eligible to participate in the trial. The choice of a microbiologically eligible population for the analyses minimizes the chance of underestimating the effect of the rifapentine-moxifloxacin in view of the non-inferiority trial design.

[12] The outcome, named 'cure' or 'favorable' outcome in the Study 31, was chosen as it was prioritized by the GDG. The definition of the favorable outcome is detailed in the Study 31 protocol and the Evidence-to Decisions tables for this GDG review.

The GDG judged that the benefits of a shorter, 4-month regimen that is as effective as the currently recommended 6-month regimen would justify the introduction of the shorter regimen as an option for treating patients with DS-TB.

Certain contextual issues were discussed that resulted in a conditional recommendation, rather than a strong one. These included:

Resources: The costs related to the use of this regimen are currently high and further research is needed on resource implications (e.g. patient and health system savings) and cost-effectiveness of the 4-month regimen. In all, 90% of the cost of medicines for the 2HPMZ/2HPM regimen comes from the rifapentine component.

Equity: Shorter-term and longer-term equity considerations were raised by GDG members. The GDG considered that in the short term, issues such as access to rifapentine, the costs of rifapentine and increased pill burden (due to the lack of fixed-dose combinations for the 4-month regimen and the fact that rifapentine was dosed at 1200 mg) may decrease equity. However, in the longer term as costs reduce and access to rifapentine (including 300 mg tablets) increases, the shorter regimen is considered likely to increase equity for patients who will have a shorter period of time engaged with the health system, potentially reducing costs associated with TB treatment, and who would be able to return to work sooner.

Acceptability and feasibility: Although patients and health-care workers may prefer a regimen of shorter duration, GDG members were concerned at the pill burden relative to the standard 6-month regimen and the potential need for fluoroquinolone DST in some settings with a high background prevalence of fluoroquinolone resistance.

Subgroup considerations

Subgroup analyses were conducted for four patient groups in order to inform the GDG discussions. The subgroup analyses presented to the GDG included people living with HIV infection, people with diabetes mellitus, people with a low body weight (body mass index < 17.9 kg/m2) and people with extensive disease (using a cut-off of >50% lung area affected) on chest radiography. The reported risk differences for these subpopulations indicated no statistically significant differences when comparing the shorter regimen to the current standard of care; however, in some subgroups the overall numbers were small in both intervention and control groups (persons with HIV and those with diabetes mellitus).

Additional pharmacokinetic analyses being undertaken by the trial investigators will be available in the future and may provide more nuanced information on drug exposures in these groups. Other subgroup analyses that were part of the trial included analyses by age group, sex, presence of cavities on chest radiography, cavity size, WHO sputum smear grade, smoking history, Xpert Ct value and Mycobacterial Growth Indicator Tube liquid culture automated system TTP (days).

Subgroups included in the recommendation

The panel suggested that the shorter regimen can be used in the subgroups for which evidence was available for review (people living with HIV infection, persons with diabetes mellitus, those with a low body weight and those with extensive disease). However, the panel also emphasized that additional research on the use of the shorter regimen in these subgroups is desirable.

People living with HIV infection: The proportion of patients living with HIV infection in the intervention and control regimen arms was 8% and only patients with CD4 count above 100 cells/mm^3 were enrolled. Of all the persons with HIV who participated in the trial (in all three arms), 95.4% were receiving antiretroviral treatment (ART). HIV-positive persons not on ART at enrollment, had planned initiation of efavirenz-based ART before or at study week 8. Persons with HIV were excluded from enrollment in the trial if, at the time of enrollment, their CD4-T cell count was known to be <100

cells/mm^3. Overall, there were nine patients who were not on ART throughout the trial follow-up in the microbiologically-eligible analysis population (4.6%); the reasons for non-initiation of ART were not clear.

People with diabetes mellitus: Additional information from pharmacokinetic analyses will be available for this population in the future which may provide more nuanced evidence on the use of the intervention and control regimens in persons with diabetes mellitus.

People with extensive TB disease: The trial reported on the presence of cavitation on chest radiograph (CXR),the extent of disease on CXR as a percentage, and cavity size (absent, < or > = 4cm).

For patients with less severe and minimal forms of TB, such as lymph node TB there was limited or no evidence on the use of the shorter regimen. However, GDG members felt that the use of the shorter regimen could be considered because favourable outcomes were reported using the shorter regimen in patients with extensive disease.

Subgroups excluded from the recommendation

However, there were also subgroups for which there was no evidence (as they were not eligible for inclusion in the trial) and therefore the use of the shorter regimen outside the research environment is not indicated in these populations. These groups include:

- people weighing less than 40 kg;
- people with certain forms of extra-pulmonary TB (such as TB meningitis, disseminated TB, osteoarticular TB, abdominal TB);
- persons living with HIV infection with a CD4 count less than 100 cells/mm^3 (NB: The trial did not include persons living with HIV infection if they had a CD4 count of less than 100 cells/mm^3 and the GDG panel expressed concerns at an increased risk of relapse in this group (also because this group is at a higher risk of disseminated TB);
- children less than 12 years of age (NB: The trial aimed to recruit people aged 12 years and above. The youngest participant was 13 years of age. Therefore, no children were included in the trial. In the microbiologically-eligible population, there were 70 and 56 participants who were under 20 years of age in the rifapentine-moxifloxacin and control arms respectively); and
- pregnant, breastfeeding and postpartum women (NB: Pregnant or breast-feeding women were excluded from the study because of uncertainties about the safety of rifapentine, moxifloxacin, and pyrazinamide in these groups. Women who became pregnant while receiving study regimens were deregistered from the study and were treated according to national TB programme or local guidelines. The women continued to receive scheduled study follow-up, were classified as being on a non-study regimen, and did not receive study radiographs. Women who became pregnant while on study follow-up (but not on study treatment) continued to receive scheduled study follow-up and did not receive study radiographs. In all cases – i.e. whether pregnant during treatment or during follow up – the outcome of the pregnancy was reported on study forms).

Implementation considerations

A number of implementation considerations were discussed by the GDG. These included the following:

Drug susceptibility testing: The panel agreed that national TB programmes should strive for universal DST. The panel also acknowledged that universal DST is not always available but rapid DST for key medicines, including rifampicin, isoniazid and the fluoroquinolones is available and is expanding at an accelerated pace. Rapid genotypic testing for TB and rifampicin resistance is recommended by WHO as an initial test for TB and, if the same sputum sample can be tested for drug susceptibility for the fluoroquinolones and isoniazid, this can facilitate assignment of the most effective regimen. This would clearly have implications in terms of logistics, laboratory workload and cost. Balancing the desired situation of having the universal DST with reality, the panel considered that although

desirable, baseline DST for fluoroquinolones would not be essential when patients with TB receive a WHO-recommended rapid molecular diagnostic test to detect rifampicin resistance. Fluoroquinolone resistance in new patients with DS-TB can reach up to 15% *[1]*, although it is significantly lower in most settings *[28-32]*. In countries with high prevalence of resistance to fluoroquinolones in new patients DST for the fluoroquinolones would be highly recommended at baseline.

Directly observed treatment: Patients in the trial received daily treatment that was directly observed at least five days per week. However, this may not be possible in programmatic settings. Directly observed treatment may be important in view of the pill burden and the lack of a fixed-dose combination formulation, and also as a measure to prevent potential amplification of drug resistance. Current WHO recommendations support the use of directly observed treatment and also other forms of patient support and, overall, even though this regimen is a 4-month one and shorter than the current standard of care, patient support remains an important element of TB programming.

Pill burden: At present, the overall pill burden will be higher for patients who will receive this 4-month regimen[13] because no fixed dose combination tablet exists for the regimen and the dose of rifapentine is high (1200 mg). This may affect acceptability by patients currently, however this situation may change in future as uptake of this regimen improves, creating a demand for the regimen and its component medicines. Wider availability of rifapentine formulation of 300 mg[14] may decrease the pill burden and facilitate the implementation of this new regimen until the FDC tablet becomes available.

Cost of medicines: The current cost of the shorter regimen is substantially[15] higher than the standard of care, mainly due to the inclusion of rifapentine. Again, this situation may change in future as uptake of the regimen improves, creating a demand for the regimen and for the medicines in it.

Administration of the shorter regimen with food may present a challenge in some settings. In the trial, a flat dose of 1200 mg of rifapentine was dosed daily, with food. This was based on: 1) demonstration of the safety of rifapentine at 1200 mg in phase I and phase II trials; 2) demonstration that body weight does not significantly affect rifapentine clearance; 3) recognition of an effect of food in increasing rifapentine absorption *[33]*; and 4) modelling predictions that the target rifapentine exposure (area under the curve [AUC] of approximately 500–600 mcg*h/L) is achievable using this strategy – see the supplementary appendix to reference *13*).

As described in the trial's statistical analysis plan, pharmacokinetic/pharmacodynamic modelling predicted that a rifapentine dose of 1200 mg without food would yield an AUC approximately the same as that of a rifapentine dose of 900 mg with a very high fat meal. Since the target rifapentine AUC lies somewhere between that achieved with a very high fat meal and a rifapentine dose of 900–1200 mg, the strategy proposed was a rifapentine dose of 1200 mg with a modest food requirement. The rationale was that a very high fat meal may not be feasible under trial or routine TB care conditions, whereas dosing with food may be feasible.

Training of health-care workers was another implementation consideration that the panel discussed. Training will be necessary when introducing the shorter regimen into a programmatic setting. However, this is a requirement for any new programmatic intervention and the ability to shorten treatment and potentially treat more patients may offset initial training investments.

Another implementation consideration discussed by the GDG concerned the choice of regimen to treat DS-TB. The GDG considered that, when choosing between the shorter 4-month regimen or the 6-month regimen, clinicians should consider eligibility criteria for the regimen and patient preference as well as local factors such as the availability of rifapentine.

---

[13] Based on estimates by the Global Drug Facility for an average weight of 55–70 kg: 1358 tablets versus 728 for whole course of treatment.

[14] Rifapentine 150mg and 300mg are both included in the WHO Model list of essential medicines: 22nd list (2021). See: https://apps.who.int/iris/bitstream/handle/10665/345533/WHO-MHP-HPS-EML-2021.02-eng.pdf (accessed 28 February 2021).

[15] Approximately 5 times (US$ 225–233 versus US$ 343), based on current estimates using weighted average prices of the Global Drug Facility.

Monitoring and evaluation

The current guidance on monitoring the response to DS-TB treatment stays the same. The panel did not recommend baseline electrocardiogram (ECG) monitoring for those receiving the shorter regimen (unless clinically indicated), and laboratory monitoring such as liver function tests would remain the same for both regimens. Some countries may have different requirements for liver function monitoring due to the "black box" warnings for moxifloxacin and these should be followed according to the country's policies.

Recommendation 7.

In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used (strong recommendation, moderate certainty of evidence) – new recommendation.

Remarks:

- Non-severe TB is defined as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern;
- Children and adolescents who do not meet the criteria for non-severe TB should receive the standard six-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of extrapulmonary TB.
- The use of ethambutol in the first two months of treatment is recommended in settings with a high prevalence of HIV[16], or of isoniazid resistance[17].

Source of recommendation

This recommendation has been developed following advice from the Guidelines Development Group convened by the WHO Global Tuberculosis Programme in May-June 2021 on the topic of the management of TB in children and adolescents. The recommendation is also featured in the consolidated guidelines module on management of tuberculosis in children and adolescents.

Justification and evidence

The majority of children with TB have less severe forms of the disease than adults. Treatment regimens that are shorter than those for adults may be effective in treating children with TB, however solid evidence to substantiate this has been lacking to date. Shorter treatment regimens can result in lower costs to families and health services, potentially less toxicity, lower risks of drug-drug interactions in children living with HIV, and fewer problems with adherence. Shorter, safe and effective treatment regimens for children with both drug-susceptible and DR-TB benefit children with TB and their families and are a key intervention to achieve the WHO's End TB Strategy targets, as well as targets related to children set during the UNGA HLM on TB in 2018. New evidence from a recently completed trial

[16] Defined as countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5% in the *Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition)* 2014.

[17] WHO does not intend to establish thresholds for low, moderate or high levels of prevalence of isoniazid resistance: NTPs will establish definitions for their own countries.

on the shortened treatment of drug-susceptible TB in children and adolescents has paved the way for new recommendations on shorter regimens for this group.

The SHINE trial (Shorter Treatment for Minimal Tuberculosis in Children) was the first and only large phase three trial to evaluate the duration of TB treatment in children with non-severe drug-susceptible TB. Therefore, evidence from the trial rather than a systematic review, was used to answer this PICO question *[34]*. The SHINE trial was a multi-centre, open-label, parallel-group, non-inferiority, randomized, controlled, two-arm trial comparing four-month (16 weeks) versus the standard six-month (24 weeks) treatment durations in children under 16 years of age with symptomatic non-severe TB. Children and young adolescents aged below 16 years were treated with rifampicin, isoniazid, pyrazinamide with or without ethambutol using WHO recommended doses, appropriate for paediatric dosing *[35]*.

PICO question: In children and adolescents with non-severe TB, should a four-month intervention regimen versus the standard six-month regimen conforming to WHO guidelines be used?

Evidence: In the SHINE trial, the primary efficacy outcome was a composite of treatment failure (including an extension of treatment beyond the replacement of missed doses, TB treatment drug changes or restarts due to suspected treatment failure), on-treatment loss-to-follow-up, TB recurrence or death by 72 weeks (from randomization), excluding children not reaching 16 weeks follow-up (modified-intention-to-treat). The non-inferiority margin for the primary efficacy outcome was 6%. The primary safety outcome was grade 3–5 adverse events recorded while on TB treatment.

The SHINE trial definition of non-severe TB was: peripheral lymph node TB or respiratory TB (including uncomplicated intrathoracic lymph node disease) confined to one lobe without cavities, no significant airway obstruction, uncomplicated pleural effusion, and no miliary TB.

The SHINE trial inclusion criteria were: children and young adolescents aged <16 years; weight ≥3 kg; no known drug-resistance; symptomatic but non-severe TB; smear negative on gastric aspirate or other respiratory sample (an Xpert MTB/RIF positive, rifampicin susceptible result was allowed);[18] clinician's decision to treat with a standard first-line regimen; not treated for TB in the previous two years; known HIV status (positive or negative). Trial exclusion criteria were: respiratory sample acid fast bacilli smear-positive (a smear-positive peripheral lymph node sample was allowed); premature birth (<37 weeks) and aged under three months; miliary TB, spinal TB, TBM, osteoarticular TB, abdominal TB, congenital TB; pre-existing, non-tuberculous disease likely to prejudice the response to, or assessment of, treatment (such as liver or kidney disease, peripheral neuropathy or cavitation); any known contraindication to taking TB drugs; known contact with a drug-resistant adult source case (including mono-resistant TB); known drug-resistance in the child; being severely ill; pregnancy.

A total of 1204 children were enrolled in the trial between July 2016 and July 2018. The median age of enrolled children was 3.5 years (range: 2 months – 15 years), 52% were male, 11% had HIV-infection, and 14% had bacteriologically confirmed TB. Retention in the trial by 72 weeks and adherence[19] to allocated TB treatment were 95% and 94%, respectively. Sixteen (2.8%) versus 18 (3.1%) children reached the primary efficacy outcome (treatment failure) in the 16- versus 24-week arms respectively, with an unadjusted difference of -0.3% (95% CI: -2.3, 1.6). Treatment success was reported in 97.1% of participants receiving the 16-week regimen versus 96.9% in those receiving the 24-week regimen (relative risk (RR): 1.00, 95% CI: 0.98–1.02). Non-inferiority of the 16-week regimen was consistent across all intention-to-treat, per-protocol and key secondary analyses. This included restricting the analysis to the 958 (80%) children that were independently adjudicated to have TB at baseline by the trial Endpoint Review Committee. A total of 7.8% of children experienced a grade 3–5 adverse

[18] In the SHINE trial, children with Xpert MTB/RIF results had very low or low semi-quantitative results, or a negative result. Xpert Ultra was not used in the SHINE trial.

[19] In the SHINE trial, adherence was defined as the proportion of children who received an adequate amount of treatment (as defined in the statistical analysis plan for both the intervention and control regimens; generally, a cut off of 80% of the allocated doses was used, within a certain time frame of starting each phase of treatment (i.e. intensive phase versus continuation phase).

event in the 16-week arm, versus 8.0% in the 24-week arm (RR: 0.98, 95% CI: 0.67–1.44). There were 115 on-treatment grade ≥3 adverse events in 95 (8%) children, 47 (8%) in the 16-week and 48 (8%) in the 24-week arm, most common being pneumonia or other chest infections (29 (25%)) or liver-related events (11 (10%)) across both arms. There were 17 grade 3 or 4 adverse reactions (considered possibly, probably or definitely) related to trial drugs, including 11 hepatic events; all adverse reactions except three occurred in the first eight weeks of treatment.

GDG considerations: The GDG judged that while the desirable effects related to this PICO question are related to treatment outcomes, shortening the duration of treatment is also important and desirable (as reducing the length of treatment could make treatment easier for children and caregivers as well as reduce cost for families and the health system). The GDG discussed that since the SHINE trial was a non-inferiority trial, no difference in unfavourable outcomes between the two arms is what the trial aimed to detect. Therefore, both desirable and undesirable effects were judged by most GDG members as trivial. Since non-inferiority of the 4-month regimen was demonstrated in the trial, the balance of effects was judged to not favour either the shorter or the longer duration of treatment. However, the GDG noted that treatment duration is a critical issue which was further considered in the context of issues such as cost, acceptability and feasibility.

The GDG also discussed that presumably, a shorter duration of treatment will reduce costs to both the health care system and to children with TB and their families. The GDG ultimately agreed on 'moderate savings' despite the varying views of the level of these savings. The GDG judged that equity was probably increased with a shorter duration of treatment. Despite no direct evidence on acceptability, the GDG judged that the shorter regimen was acceptable to stakeholders.

In addition, the GDG felt that, in the absence of exposure to DR-TB, access to CXR would help distinguish between non-severe and severe disease. However, the panel recognized that access to CXR is often limited or quality of CXR and capacity for interpretation is insufficient at lower levels of the health care system, which may have equity implications. Therefore, feasibility was judged to vary by setting. The GDG noted that it is critically important to clearly define "non-severe" disease and that NTPs be encouraged to scale up access to quality CXR and train health care providers in its interpretation. Overall, the GDG judged that if the severity of TB disease in children can be adequately determined under programmatic conditions, then implementation of a four-month regimen is highly feasible.

Subgroup considerations

Children with peripheral lymph node TB: Although the number of children with peripheral lymph node TB in the SHINE trial were small (N=19 in the 16-week arm and N=21 in the 24-week arm), there was no difference in the proportion of unfavourable outcomes between the two arms. The SHINE trial also found that 16 weeks of treatment was non-inferior compared to 24 weeks of treatment among children with both peripheral lymph node disease and pulmonary disease (N=182 in the 16-week arm and N=171 in the 24-week arm). These results may provide reassurance to clinicians regarding a seemingly delayed clinical response to TB treatment, frequently seen in children with peripheral lymph node TB (where lymph nodes remain enlarged even after treatment).

Children and adolescents living with HIV infection (CALHIV): CALHIV were eligible for enrolment in the SHINE trial; 65 (11%) CALHIV were enrolled in the 16-week arm and 62 (10%) in the 24-week arm. 49% of CALHIV in the 16-week arm and 43% in the 24-week arm were on antiretroviral treatment at the time of enrolment. 20% of CALHIV in both arms had a CD4 count of less than 200 cells per mm^3. 51% of CALHIV in the 16-week arm and 63% in the 24-week arm were classified as severe as per the WHO immunological classification for established HIV infection *[36]*. In this subgroup, the 16-week regimen was non-inferior as compared to the 24-week regimen as well, although the 95% confidence interval for the difference in the unfavourable rate compared to the control arm was wide (risk difference -4.3, 95% CI -14.9 to 6.2).

In view of the limited evidence, clinicians may consider treating CALHIV with non-severe TB for four months, depending on the degree of immunosuppression and ART status, as well as the presence of other opportunistic infections. These children and adolescents will need to be monitored closely, especially at four months of treatment, and treatment extended to 6 months if there is insufficient progress.

Children with severe acute malnutrition (SAM): In the SHINE trial, SAM was defined as weight-for-height Z-score (WHZ) <−3 or MUAC <115 mm [37]. Thirty children with SAM (5%) were included in the 16-week arm and 33 (5%) in the 24-week arm. No separate sub-group analysis was therefore conducted for children with SAM. In view of the insufficient evidence on this subgroup, and as SAM is defined as a danger sign, children with SAM and non-severe TB should preferably receive 6 months of TB treatment.

Infants <3 months of age and/or weighing < 3kg: Infants <3 months of age and infants weighing <3 kg (including premature birth (<37 weeks) were not eligible for inclusion in the SHINE trial. No new data on the treatment of congenital TB and very young infants (aged 0–3 months) with TB disease was received following a call for data. Therefore, infants aged 0–3 months with suspected or confirmed PTB or tuberculous peripheral lymphadenitis should be promptly treated with the six-month treatment regimen (2HRZ(E)/4HR), as per the existing recommendation from the 2014 *Guidance for national tuberculosis programmes on the management of tuberculosis in children [19]*. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in the management of paediatric TB.

Children treated for TB in the past two years: Given the increased risk of treatment failure and of drug resistance, children and adolescents treated in the preceding two years were not eligible for inclusion in the SHINE trial; they should be treated with the six-month treatment regimen (2HRZ(E)/4HR).

Implementation considerations

Assessing severity of disease: The feasibility of assessing the severity of TB disease, particularly in settings without access to CXR or capacity for CXR interpretation and WHO-recommended diagnostic tests was identified as a major implementation consideration. Chest radiography was identified by the GDG as a critical tool to evaluate the severity of intrathoracic disease. As indicated under the recommendation remarks, non-severe intrathoracic or PTB disease refers to: intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease confined to one lobe of the lungs and without a miliary pattern. Extensive or advanced disease in children under 15 years of age is usually defined by the presence of cavities or bilateral disease on CXR [38]. NTPs are encouraged to scale up access to quality CXR and provide training to health care providers in its interpretation. Out-of-pocket expenses for CXR pose a potential barrier to TB diagnosis and access to shorter regimen for eligible children and young adolescents. In the SHINE trial, children who were Xpert MTB/RIF positive, but sputum smear-negative were eligible for inclusion. The 85 children (7%) who were Xpert MTB/RIF positive (45 in the four-month arm and 40 in the six-month arm), had very low or low semi-quantitative Xpert MTB/RIF results.

Detailed implementation guidance is provided in the *Operational handbook on the management of tuberculosis in children and adolescents*, taking into consideration differences in the health care system and country context, including the availability of diagnostic tools to make a diagnosis and to assess disease severity. While access to CXR is an important implementation consideration, it should not be a barrier for children and adolescents in lower resourced settings to benefit from the shorter regimen. The implementation guidance in the operational handbook comprises criteria for assessing disease severity, including clinical criteria in the absence of CXR or rapid diagnostics or other bacteriological tests, to determine eligibility for the shorter regimen. Children with Xpert MTB/RIF or Ultra results

that are trace, very low or low, who meet radiographical or clinical criteria for non-severe TB, can be treated with the four-month regimen.

Continuum between TB infection and disease: An additional implementation consideration is the concept that a continuum exists between TB infection, non-severe and more severe forms of TB disease in children. Shorter treatment regimens for drug-susceptible TB are now very similar to recently recommended shorter regimens for the treatment of TB infection, in terms of duration and composition, in particular the regimen that consists of three months of daily isoniazid and rifampicin (3HR) *[39]*. This implies that incorrectly diagnosing a child who has TB infection as having non-severe TB disease may not have severe consequences.

Contact investigation: Another implementation consideration is the scale up contact investigation approaches, which can improve early case detection of children with non-severe disease who may benefit from the 4-month regimen.

Use of ethambutol in the intensive phase of treatment: Children and young adolescents with non-severe TB who live in settings with low HIV prevalence or a low prevalence of isoniazid resistance and those who are HIV negative can be treated with a three-drug regimen (HRZ) for two months, followed by two months of HR. Children and young adolescents with non-severe TB who are living in settings where the prevalence of HIV is high[20] and/or the prevalence of isoniazid resistance is high[21] should be treated with HRZE for two months followed by HR for two months. In the SHINE trial, ethambutol was used in line with these recommendations as per national guidelines and all CALHIV received ethambutol as part of their treatment. For the six-month regimen used to treat more severe forms of TB, it is recommended to add ethambutol to the regimen (i.e. 4HRZE/2HR).

Child-friendly formulations: NTPs are encouraged to prioritize the use of child-friendly fixed dose combination (FDC) formulations for TB treatment in children up to 25 kg body weight, such as: the 3-FDC HRZ 50/75/150 mg with or without the addition of dispersible ethambutol, and the 2-FDC HR 50/75 mg (available from the Stop TB Partnership's Global Drug Facility (GDF)). Capacity building of health care workers at all levels of the health system on diagnostic approaches (including treatment decision algorithms), eligibility for the four-month regimen and monitoring of children on first-line TB treatment will also be critical factors in the successful implementation of the shorter regimen.

Treatment of severe pulmonary TB in children and young adolescents: Children and young adolescents with forms of PTB that do not meet the eligibility criteria for the four-month regimen should be treated with a standard six-month regimen that includes a fourth drug (ethambutol) in the intensive phase (such as 2HRZE/4HR).

Treatment options for adolescents from 12 years of age: Another implementation consideration is that adolescents aged 12 years and above with TB can benefit from the four-month regimen that consists of isoniazid, rifapentine, moxifloxacin and pyrazinamide (HPMZ), which is now conditionally recommended by WHO (see Recommendation 6 in the current document). Adolescents aged between 12 and 16 years therefore have three options for treatment: the four-month HPMZ regimen, the four-month 2HRZ(E)/2HR regimen, and the standard six-month 2HRZ(E)/4HR regimen. Adolescents from 16 years of age were not included in the SHINE trial and therefore have two options: the four-month HPMZ regimen and the standard six-month 2HRZE/4HR regimen.

Choosing an appropriate regimen for this age group will depend on clinical factors (such as the presence of severe disease or if living with HIV, ART status and CD4 count) as well as contextual factors (including the availability of the HPMZ regimen in the country).

---

[20] This level of resistance was defined as countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5% in the Guidance for national tuberculosis programmes on the management of tuberculosis in children (second edition) 2014.

[21] WHO does not intend to establish thresholds for low, moderate or high levels of prevalence of isoniazid resistance; instead NTPs will establish definitions for their own countries.

Monitoring and evaluation

The clinical monitoring requirements for the shorter regimen remain the same as for the six-month regimen and treatment outcomes are determined at the end of the four-month regimen.

Should there be insufficient clinical improvement after completion of the four-month regimen, the clinician may decide to extend treatment to six months while considering alternative diagnoses, including DR-TB.

Monitoring for potential relapse is a priority for shorter regimens especially when they are introduced into programmatic settings. Therefore, follow-up of children and young adolescents for up to 12 months after completion of the four-month regimen is important.

Drug-susceptible TB treatment and ART in people living with HIV

Recommendation 8.

It is recommended that TB patients who are living with HIV should receive at least the same duration of daily TB treatment as HIV-negative TB patients (strong recommendation, high certainty of evidence)

Source of recommendation

This recommendation was first put forward in 2010 and considered valid in the guidelines update of 2017 (see mapping of recommendations in Annex). The recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.

Justification and evidence

A systematic review and meta-analysis of 6 randomized controlled trials and 21 cohort studies provided pooled estimates of failure, relapse and death by duration of rifampicin, and daily intensive phase versus intermittent throughout *[40]*. The systematic review revealed a marked and significant reduction in failure and relapse in the arms where some or all patients received ART. In a regression model, treatment failure or relapse was 1.8–2.5 times more likely with intermittent rather than daily dosing in the intensive phase. Compared with 8 or more months of rifampicin, 2-month rifampicin regimens carried a 3-fold higher risk of relapse and 6-month regimens carried a 2.2 -fold higher risk. Extending treatment beyond 6 months is recommended by some expert groups in certain persons living with HIV and the meta-analysis showed that this is associated with significantly lower relapse rates. However, several other considerations were given greater weight. Separate regimens for TB patients living with or without HIV would be very challenging in operational terms and could create stigma. Other potential harms of extending treatment are acquired resistance to rifampicin, and a longer period during which ART options are limited (because of ART–rifampicin interactions).

Recommendation 9.

ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.[a]

Adults and adolescents (strong recommendation, low to moderate certainty of evidence;

Children and infants (strong recommendation, very low certainty of evidence)

[a.] Except when signs and symptoms of meningitis are present.

Source of recommendation

This recommendation is from WHO's *Consolidated guidelines on HIV infection, testing, treatment, service delivery and monitoring: recommendations for a public health approach [41]*. The background and history of this recommendation is provided below, while the detailed rationale and supporting evidence can be found in the source document.

The recommendation applies to both children and adults but the strength of the recommendation and certainty of the evidence differ for each group because of the difference in the available data for the reviews. One specific exception that is highlighted in this recommendation relates to situations in which signs and symptoms of meningitis are present. Caution is needed regarding people who are living with HIV and who have TB meningitis because immediate ART is significantly associated with more severe adverse events. Thus, it might be a consideration to delay ART for 4–8 weeks after TB treatment is initiated in such situations.

The use of corticosteroids as adjuvant treatment for TB meningitis still applies in these situations.

Background

Since 2010, WHO has recommended that ART be started as soon as possible within eight weeks of initiating TB treatment (strong recommendation, high certainty of evidence) *[42]*. In 2012, WHO added a recommendation to initiate ART within two weeks among those with a CD4 count less than or equal to 50 cells/mm^3 (except for children for whom previous recommendations remained unchanged because of the lack of specific evidence) *[43]*. In 2017, on the basis of a systematic review of evidence that earlier ART initiation resulted in reduced morbidity and mortality *[44]*, WHO recommended offering rapid ART initiation within one week, and on the same day if ready, for all people diagnosed with HIV – including adults, adolescents and children [44] – with stated cautions for those with signs and symptoms of TB meningitis.

The use of adjuvant steroids in the treatment of TB meningitis and pericarditis

Recommendation 10.

In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used (strong recommendation, moderate certainty of evidence).

Recommendation 11.

In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used (conditional recommendation, very low certainty of evidence).

Source of recommendation

These recommendations were first put forward in the guidelines update of 2017 (see mapping of recommendations in Annex). They are copied without modification into this consolidated document and appear exactly as in the 2017 guidelines.

Justification

In patients with tuberculous meningitis, evidence from randomized controlled trials in the systematic review *[45–49]* showed lower rates of mortality, death or severe disability, and disease relapse when patients were treated with steroids in addition to anti-TB treatment. The benefits in terms of mortality increased with the increasing TB meningitis stage (i.e. increasing severity of disease). Additionally, rates of adverse events and severe adverse events, including severe hepatitis, were lower in the patients receiving steroids.

In patients with tuberculous pericarditis, evidence from studies in the systematic review *[50–57]* showed a benefit to steroid treatment with regard to death, constrictive pericarditis and treatment adherence. When the studies were considered individually, the largest (1400 patients) and most recent study – the IMPI study *[52]* – showed no benefit with steroids. However, a complicating factor in these findings is HIV infection. In the IMPI study, 67% of subjects were HIV-positive and only 14% were on ART. This raises the question as to whether immunosuppressed patients may have had a different benefit from steroids when compared to HIV-negative people or persons living with HIV who are on ART. In the IMPI study, a supplemental analysis was done of the HIV-negative patients only and a small mortality benefit was shown with steroid treatment. However, the relationship between HIV infection and steroids is complex. In another smaller study of 58 subjects, all of whom were HIV-positive, steroids were found to reduce mortality *[53]*. It is of note that the other studies in the review did not address HIV and mortality.

The panel considered that the benefit in preventing constrictive pericarditis outweighed the potential harms of corticosteroid therapy.

Subgroup considerations

Steroids should be given regardless of the severity of meningitis. With regard to the use of steroids in tuberculous pericarditis, in one study an increase in HIV-related cancers (non-Hodgkins' lymphoma and Kaposi sarcoma) was observed *[52]*. However, this increase appears to be caused by co-administration of immunotherapy (*M. indicus pranii*).

Implementation considerations

Practitioners should give oral steroids if intravenous formulations are not available.

Monitoring and evaluation

There are no additional recommendations beyond the standard of care.

Research priorities

The GDGs discussed future research and highlighted a number of priorities.

1. ***The effectiveness of fixed-dose combination TB treatment when compared to separate drug formulations in patients with DS-TB disease***
    - Additional research on the reasons why FDC formulations did not show a clear benefit over separate drug formulations.
    - Pharmacokinetic studies of the bioavailability of FDCs versus separate drug formulations and better development of weight band categories for drug dosing.
    - The optimal dose of rifampicin, including the use of different drug formulations in all age groups.
    - Additional qualitative studies detailing adherence to medication.
    - Additional work on FDC formulations to further decrease the pill burden, especially among patients with comorbidities.

2. ***The use of steroids in the treatment regimen of extrapulmonary TB disease***
    - The optimal steroid dose for TB meningitis (including different drug formulations).
    - The optimal steroid duration for TB meningitis and if this duration differs between different grades of meningitis.
    - The different effects of steroids on people who are HIV-positive or HIV-negative, or who are being treated (or not) with ART.
    - The relationship between steroid treatment and cancer risk, with reference to the Mayosi et al. study on pericarditis *[50]*.

3. ***4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide for drug-susceptible pulmonary TB***
    - Acquisition of drug resistance for Mycobacterium tuberculosis and for other bacteria while on treatment with a 4-month regimen.
    - The efficacy of the regimen for patients with extra-pulmonary TB.
    - Pharmacokinetic, safety and tolerability studies in younger adolescents and children. A pharmacokinetic sub-study in adults was initiated alongside the trial, and the results were expected within months of the GDG meeting.
    - The cost-effectiveness of the shorter regimen.
    - Considerations regarding the impact of the 4-month regimen on equity.
    - The acceptability of the shorter 4-month regimen, particularly for patients.
    - The use of this regimen in specific subgroups – including pregnant and lactating women, children aged less than 12 years, HIV-positive individuals with a CD4 count lower than 100 cells/mm^3, people with diabetes mellitus and people with a body weight less than 40 kg.
    - Dosing considerations for people weighing less than 40 kg.
    - The use and acceptability of FDC formulations for the shorter 4-month regimen.
    - Operational research on directly observed treatment versus self-administered therapy.
    - Treatment adherence and completion in operational settings.

References

1. Global tuberculosis report. Geneva: World Health Organization; 2020 (https://www.who.int/publications-detail-redirect/9789240013131, accessed 3 March 2022).
2. The end TB strategy. Geneva: World Health Organization; 2015 (https://www.who.int/publications-detail-redirect/WHO-HTM-TB-2015.19, accessed 3 March 2022).
3. Guidelines for treatment of drug-susceptible tuberculosis and patient care. Geneva: World Health Organization; 2017 (https://www.who.int/publications-detail-redirect/9789241550000, accessed 3 March 2022).
4. Treatment of tuberculosis, guidelines for national programmes, fourth edition. Geneva: World Health Organization; 2010 (https://www.who.int/publications-detail-redirect/9789241547833, accessed 3 March 2022).
5. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. Int J Tuberc Lung Dis. 1999;3(10 Suppl 2):S231–79.
6. WHO handbook for guideline development. Geneva: World Health Organization; 2014:167 (https://apps.who.int/iris/handle/10665/145714, accessed 3 March 2022).
7. About the WHO Guidelines Review Committee. Geneva: World Health Organization; 2021 (https://www.who.int/groups/guidelines-review-committee, accessed 3 March 2022).
8. Guyatt GH, Oxman AD, Gunn EV, Kunz R, Falck-Ytter Y, Alonso-Coello P et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ. 2008;336(7650):924–6.
9. Menzies D, Benedetti A, Paydar A, Martin I, Royce S, Pal M et al. Effect of duration and intermittency of rifampin on tuberculosis treatment outcomes: a systematic review and meta-analysis. PLoS Med. 2009;6(9):e1000146. doi: 10.1371/journal.pmed.1000146.
10. Updated recommendations on HIV prevention, infant diagnosis, antiretroviral initiation and monitoring. Geneva: World Health Organization; 2021 (https://www.who.int/publications-detail-redirect/9789240022232, accessed 3 March 2022).
11. Menzies D, Benedetti A, Paydar A, Royce S, Pal M, Burman W et al. Standardized treatment of active tuberculosis in patients with previous treatment and/or with mono-resistance to isoniazid: a systematic review and meta-analysis. PLoS Med. 2009;6(9):e1000150. doi:10.1371/journal.pmed.1000150.
12. Jindani A, Nunn AJ, Enarson DA. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomised trial. Lancet. 2004;364(9441):1244–51.
13. Gillespie SH, Crook AM, McHugh TD, Mendel CM, Meredith SK et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med. 2014;371(17):1577–87. doi:10.1056/NEJMoa1407426.
14. Merle CS, Fielding K, Bah Sow O, Gninafon N, Lo MB, Mthiyane T et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. N Engl J Med. 2014;371(17):1588–98. doi:10.1056/NEJMoa1315817.
15. Blanc FX, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med. 2011;365(16):1471–81. doi:10.1056/NEJMoa1013911.

16. Johnson JL, Hadad DJ, Dietze R, Noia Maciel EL, Sewali B, Gitta P et al. Shortening treatment in adults with noncavitary tuberculosis and 2-month culture conversion. Am J Respir Crit Care Med. 2009;180(6):558–63.

17. Lienhardt C, Cook SV, Burgos M, Yorke-Edwards V, Rigouts L, Anyo G et al. Efficacy and safety of a 4-drug fixed-dose combination regimen compared with separate drugs for treatment of pulmonary tuberculosis: the Study C randomized controlled trial. JAMA. 2011;305(14):1415–23. doi:10.1001/jama.2011.436.

18. Swaminathan S, Narendran G, Venkatesan P, Iliayas S, Santhanakrishnan R, Aravindan Menon P et al. Efficacy of a 6-month versus 9-month intermittent treatment regimen in HIV-infected patients with tuberculosis: a randomized clinical trial. Am J Respir Crit Care Med. 2010;181(7):743–51. doi:10.1164/rccm.200903–0439OC.

19. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: World Health Organization; 2014 (https://www.who.int/publications-detail-redirect/9789241548748, accessed 3 March 2022).

20. Albanna AS, Smith BM, Cowan D, Menzies D. Fixed-dose combination antituberculosis therapy: a systematic review and meta-analysis. Eur Respir J. 2013;42(3):721–32. doi:10.1183/09031936.00180612.

21. Gallardo CR, Comas DR, Valderrama Rodríguez A, Roqué i Figuls M, Parker LA, Caylà J et al. Fixed-dose combinations of drugs versus single-drug formulations for treating pulmonary tuberculosis. Cochrane Database Syst Rev. 2016(5):CD009913. doi:10.1002/14651858.CD009913.pub2.

22. Blomberg B, Spinaci S, Fourie B, Laing R. The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. Bull World Health Organ. 2001;79(1):61–8 (https://apps.who.int/iris/handle/10665/268235, accessed 3 March 2022).

23. Milan-Segovia RC, Domínguez-Ramírez AM, Jung-Cook H, Magaña-Aquino M, Romero-Méndez MC, Medellín-Garibay SE et al. Relative bioavailability of rifampicin in a three-drug fixed-dose combination formulation. Int J Tuberc Lung Dis. 2010;14(11):1454–60.

24. Hao L-H, Guo S-C, Liu C-C, Zhu H, Wang B, Fu L et al. Comparative bioavailability of rifampicin and isoniazid in fixed-dose combinations and single-drug formulations. Int J Tuberc Lung Dis. 2014;18(12):1505–12. doi:10.5588/ijtld.13.0647.

25. Aung KJM, Declercq E, Ali MdA, Naha S, Datta Roy SC, Taled NMdA et al. Extension of the intensive phase reduces relapse but not failure in a regimen with rifampicin throughout. Int J Tuberc Lung Dis. 2012;16(4):455–61. doi:10.5588/ijtld.11.0216.

26. Jindani A, Harrison TS, Nunn AJ, Phillips PJ, Churchyard GJ, Charalambous S et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. N Engl J Med. 2014;371(17):1599–608. doi:10.1056/NEJMoa1314210.

27. Dorman SE, Nahid P, Kurbatova EB, Phillips PJ, Bryant K, Dooley KE et al. Four-month rifapentine regimens with or without moxifloxacin for tuberculosis. N Engl J Med. 2021;384(18):1705–18. doi:10.1056/NEJMoa2033400.

28. Ismail NA, Mvusi L, Nanoo A, Dreyer A, Omar SV, Babatunde S et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. Lancet Infect Dis. 2018;18(7):779–87. doi:10.1016/S1473–3099(18)30222–6.

29. Kayomo MK, Mbula VN, Aloni M, André E, Riogouts L, Boutachkourt F et al. Targeted next-generation sequencing of sputum for diagnosis of drug-resistant TB: results of a national survey in Democratic Republic of the Congo. Sci Rep. 2020;10(1):10786.

30. Lim DR, Dean AS, Taguinod-Santiago MR, Borbe-Reyes A, Cabibbe AM, Zignol M et al. Low prevalence of fluoroquinolone resistance among patients with tuberculosis in the Philippines: results of a national survey. Eur Respir J. 2018;51(3). doi:10.1183/13993003.02571–2017.

31. Mesfin AB, Araia ZZ, Beyene HN, Mebrahtu AH, Suud NN, Berhane YM et al. First molecular-based anti-TB drug resistance survey in Eritrea. Int J Tuberc Lung Dis. 2021;25(1):43–51. doi:10.5588/ijtld.20.0558.

32. Zignol M, Dean AS, Alikhanova N, Andres S, Cabibbe AM, Cirillo DM et al. Population-based resistance of Mycobacterium tuberculosis isolates to pyrazinamide and fluoroquinolones: results from a multicountry surveillance project. Lancet Infect Dis. 2016;16(10):1185–92. doi:10.1016/S1473–3099(16)30190–6.

33. Zvada SP, Van Der Walt J-S, Smith PJ, Fourie PB, Roscigno G, Mitchison D et al. Effects of four different meal types on the population pharmacokinetics of single-dose rifapentine in healthy male volunteers. Antimicrob Agents Chemother. 2010;54(8):3390–4. doi:10.1128/AAC.00345–10.

34. Turkova, A., et al., *Shorter treatment for non-severe tuberculosis in African and Indian children.* N. Engl. J. Med, 2022.

35. Chabala, C., et al., *Shorter treatment for minimal tuberculosis (TB) in children (SHINE): a study protocol for a randomised controlled trial.* Trials, 2018. 19(1): p. 1–12.

36. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva: World Health Organization; 2007 (https://apps.who.int/iris/handle/10665/43699, accessed 3 March 2022).

37. Guideline: updates on the management of severe acute malnutrition in infants and children. Geneva: World Health Organization; 2013 (https://www.who.int/publications-detail-redirect/9789241506328, accessed 3 March 2022).

38. WHO operational handbook on tuberculosis. Module 4: Treatment – Drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications-detail-redirect/9789240006997, accessed 3 March 2022).

39. WHO consolidated guidelines on tuberculosis. Module 1: Prevention – tuberculosis preventive treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications-detail-redirect/9789240001503, accessed 3 March 2022).

40. Khan FA, Minion J, Pai M, Rovce S, Burman W, Harries AD et al. Treatment of active tuberculosis in HIV-coinfected patients: a systematic review and meta-analysis. Clin Infect Dis. 2010;50(9):1288–99. doi:10.1086/651686.

41. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021 (https://www.who.int/publications-detail-redirect/9789240031593, accessed 3 March 2022).

42. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach – 2010 revision. Geneva: World Health Organization; 2010 (https://apps.who.int/iris/handle/10665/44379, accessed 3 March 2022).

43. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/208825, accessed 3 March 2022).

44. Guidelines for managing advanced HIV disease and rapid initiation of antiretroviral therapy. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/handle/10665/255884, accessed 3 March 2022).

45. Chotmongkol V, Jitpimolmard S, Thavornpitak Y. Corticosteroid in tuberculous meningitis. J Med Assoc Thai. 1996;79(2):83–90.

46. Kumarvelu S, Prasad K, Khosla A, Behari M, Ahuja GK. Randomized controlled trial of dexamethasone in tuberculous meningitis. Tuber Lung Dis. 1994;75(3):203–7. doi:10.1016/0962–8479(94)90009–4.

47. Malhotra HS, Garg RK, Singh MK, Agarwal A, Verma R. Corticosteroids (dexamethasone versus intravenous methylprednisolone) in patients with tuberculous meningitis. Ann Trop Med Parasitol. 2009;103(7):625–34. doi:10.1179/000349809X12502035776315.

48. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. Pediatrics. 1997;99(2):226–31. doi:10.1542/peds.99.2.226.

49. Thwaites GE, Nguyen DB, Nguyen HD, Hoang TQ, Do TTO, Nguyen TCT et al. Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. N Engl J Med. 2004;351(17):1741–51. doi:10.1056/NEJMoa040573.

50. Mayosi BM, Ntsekhe M, Volmink JA, Commerford PJ. Interventions for treating tuberculous pericarditis. Cochrane Database Syst Rev. 2002(4):CD000526. doi:10.1002/14651858.CD000526.

51. Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2013;13(3):223–37. doi:10.1016/S1473–3099(12)70321–3.

52. Mayosi BM, Ntsekhe M, Bosch J, Pandie S, Jung H, Gumedze F et al. Prednisolone and *Mycobacterium indicus pranii* in tuberculous pericarditis. N Engl J Med. 2014;371(12):1121–30. doi:10.1056/NEJMoa1407380.

53. Hakim JG, Ternouth I, Mushangi E, Siziya S, Robertson V, Malin A. Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. Heart. 2000;84(2):183–8. doi:10.1136/heart.84.2.183.

54. Reuter H, Burgess LJ, Louw VJ, Doubell AF. Experience with adjunctive corticosteroids in managing tuberculous pericarditis. Cardiovasc J S Afr. 2006;17(5):233–8.

55. Schrire V. Experience with pericarditis at Groote Schuur Hospital, Cape Town: an analysis of one hundred and sixty cases studied over a six-year period. S Afr Med J. 1959;33:810–7.

56. Strang JI, Kakaza HH, Gibson DG, Allen BW, Mitchison DA, Evans DJ et al. Controlled clinical trial of complete open surgical drainage and of prednisolone in treatment of tuberculous pericardial effusion in Transkei. Lancet. 1988;2(8614):759–64. doi:10.1016/s0140–6736(88)92415–4.

57. Strang JI, Kakaza HH, Gibson DG, Girling DJ, Nunn AJ, Fox W et al. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. Lancet. 1987;2(8573):1418–22. doi:10.1016/s0140–6736(87)91127–5.

Annex. Summary of changes in policy on DS-TB treatment since 2010 and mapping of recommendations in consolidated DS-TB guidelines

Treatment of DS-TB using 6-month regimen		
Treatment of tuberculosis, guidelines for national programmes, fourth edition 2010 *(1)*	**Guidelines for treatment of drug-susceptible tuberculosis and patient care. 2017 *(2)***	**Consolidated guidelines on tuberculosis Module 4: Treatment Drug-susceptible tuberculosis treatment.**
(Recommendation 1.1) New patients with pulmonary TB should receive a regimen containing 6 months of rifampicin: 2HRZE/4HR (strong recommendation, high certainty of evidence)	Remained valid	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.** Recommendation 1
(Recommendation 1.2) The 2HRZE/6HE treatment regimen should be phased out (strong recommendation, high certainty of evidence)	Remained valid	**Redundant. The 2HRZE/6HE regimen is not recommended since 2010 and has been phased out**
(Recommendation 2.1) Wherever feasible, the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy (strong recommendation, high certainty of evidence)	Remained valid	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.** Recommendation 2

(Recommendation 2.1A) New patients with pulmonary TB may receive a daily intensive phase followed by a three-times-weekly continuation phase [2HRZE/4(HR)$_3$], provided that each dose is directly observed (conditional recommendation, high or moderate certainty of evidence)	UPDATED (Recommendation 1.3) In all patients with drug-susceptible pulmonary TB, the use of thrice-weekly dosing is not recommended in both the intensive and continuation phases of therapy, and daily dosing remains the recommended dosing frequency (conditional recommendation, very low certainty of evidence).	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2017 guidelines update. This recommendation complements recommendation 2** Recommendation 3
(Recommendation 2.1B) Three-times-weekly dosing throughout therapy [2(HRZE)$_3$/4(HR)$_3$] may be used as another alternative to daily dosing, provided that every dose is directly observed, and the patient is NOT living with HIV or living in an HIV-prevalent setting (conditional recommendation, high or moderate certainty of evidence)		
No recommendation	NEW RECOMMENDATION (Recommendation 1.2) The use of **FDC tablets** is recommended over separate drug formulations in the treatment of patients with drug-susceptible TB (conditional recommendation, low certainty of evidence)	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines.** Recommendation 4
(Recommendation 2.2) New patients with TB should not receive twice-weekly dosing for the full course of treatment unless this is done in the context of formal research (strong recommendation, high certainty of evidence)	Remained valid	**Redundant** **All treatment of DS-TB is daily as stated in recommendations 2, and 3.**

(Recommendation 3) In populations with known or suspected high levels of isoniazid resistance, new TB patients may receive HRE as therapy in the continuation phase as an acceptable alternative to HR (conditional recommendation, insufficient evidence, expert opinion based)	Remained valid	**Redundant** **New policy on treatment of isoniazid-resistant TB in consolidated guidelines on DR-TB treatment 2020.** ***(3)***
(Recommendation 5.1) For smear-positive pulmonary TB patients treated with first-line drugs, sputum smear microscopy may be performed at completion of the intensive phase of treatment (conditional recommendation, high or moderate certainty of evidence)	Remained valid	**Redundant** **Recommendation was based on evidence derived from studies using 6-month regimens.** **Bacteriological monitoring of DS-TB treatment is included in the WHO operational handbook.**
(Recommendation 5.2) In new patients, if the specimen obtained at the end of the intensive phase (month 2) is smear-positive, sputum smear microscopy should optimally be obtained at the end of the month 3 (strong recommendation, high certainty of evidence)	Remained valid	**Redundant** **Recommendation was based on evidence derived from studies using 6-month regimens.** **Bacteriological monitoring of DS-TB treatment is included in the WHO operational handbook.**
(Recommendation 5.3) In new patients, if the specimen obtained at the end of month 3 is smear-positive, sputum culture and drug susceptibility testing (DST) should be performed (strong recommendation, high certainty of evidence)	Remained valid	**Redundant** **Rapid molecular tests are recommended for use as initial tests for TB and for rifampicin-resistance in people with symptoms of TB, without or with prior history of TB.** **Bacteriological monitoring of DS-TB treatment is included in the WHO operational handbook.**

(Recommendation 5.4) In previously treated patients, if the specimen obtained at the end of the intensive phase (month 3) is smear-positive, sputum culture and drug susceptibility testing (DST) should be performed (strong recommendation, high certainty of evidence)	Remained valid	**Redundant** **Rapid molecular tests are recommended for use as initial tests for TB and for rifampicin-resistance in people with symptoms of TB, without or with prior history of TB.** **Bacteriological monitoring of DS-TB treatment is included in the WHO operational Handbook.**
(Recommendation 6) In new pulmonary TB patients treated with the regimen containing rifampicin throughout treatment, if a positive sputum smear is found at completion of the intensive phase, **the extension of the intensive phase is not recommended** (strong recommendation, high certainty of evidence)	Remained valid	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2010 guidelines. It remains valid for 6 months regimens due to evidence used for review. Extension of the 4-month regimens is not part of pertinent recommendations** **Recommendation 5**
(Recommendation 7.1) Specimens for culture and drug-susceptibility testing should be obtained from all previously treated TB patients at or before the start of treatment. Drug-susceptibility testing should be performed for at least isoniazid and rifampicin (based on expert opinion)	Remained valid	**Expert opinion has been changing over time influenced by new evidence, experience and changing policies. Therefore, if not redundant and still relevant these statements are featured in the WHO operational handbook.**
(Recommendation 7.2) In settings where rapid molecular-based drug susceptibility testing is available, the results should guide the choice of regimen (expert opinion based)	Remained valid	**Expert opinion has been changing over time influenced by new evidence, experience and changing policies. Therefore, if not redundant and still relevant these statements are featured in the WHO operational handbook.**

(Recommendation 7.3.1) In settings where rapid molecular-based drug susceptibility testing results are not routinely available to guide the management of individual patients, TB patients whose treatment has failed or other patient groups with high likelihood of MDR-TB should be started on an empirical MDR regimen (expert opinion based)	Remained valid	**Expert opinion has been changing over time influenced by new evidence, experience and changing policies. Therefore, if not redundant and still relevant these statements are featured in the WHO operational handbook.**
(Recommendation 7.3.2) In settings where rapid molecular-based drug susceptibility testing results are not routinely available to guide the management of individual patients, TB patients returning after defaulting or relapsing from their first treatment course may receive the retreatment regimen containing first-line drugs 2HRZES/1HRZE/5HRE if country-specific data show low or medium levels of MDR in these patients or if such data are unavailable (expert opinion based)	UPDATED (recommendation 1.7) In patients who require TB retreatment, the Category II regimen should no longer be prescribed, and drug-susceptibility testing should be conducted to inform the choice of treatment regimen (Good practice statement)	**2017 good practice statement included in the operational handbook**
(Recommendation 7.4) In settings where drug-susceptibility testing results are not yet routinely available to guide the management of individual patients, the empirical regimens will continue throughout the course of treatment (based on expert opinion)	Remained valid	**Expert opinion has been changing over time influenced by new evidence, experience and changing policies. Therefore, if not redundant and still relevant these statements are featured in the WHO operational handbook.**
(Recommendation 7.5) National TB control programmes should obtain and use their country-specific drug resistance data on failure, relapse and loss to follow-up of patient groups to determine the levels of MDR-TB (based on expert opinion)	Remained valid	**Expert opinion has been changing over time influenced by new evidence, experience and changing policies. Therefore, if not redundant and still relevant these statements are featured in the WHO operational handbook.**

Treatment of DS-TB using 4-month regimens		
No recommendation	NEW RECOMMENDATION (Recommendation 1.1) In patients with drug-susceptible pulmonary TB, 4-month fluoroquinolone-containing regimens should not be used and the 6-month rifampicin-based regimen 2HRZE/4HR remains the recommended regimen (strong recommendation, moderate certainty of evidence)	**UPDATED AND NEW RECOMMENDATION** **Patients aged 12 years or older with drug-susceptible pulmonary TB, may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide** **(conditional recommendation, moderate certainty of evidence)** Recommendation 6
No recommendation	No recommendation	**NEW RECOMMENDATION** **In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used** **(strong recommendation, moderate certainty of evidence)** Recommendation 7

DS-TB treatment and ART in people living with HIV		
(Recommendation 4.1) TB patients with known positive HIV status and all TB patients living in HIV-prevalent settings should receive daily TB treatment at least during the intensive phase (strong recommendation, high certainty of evidence) (recommendation 4.2) For the continuation phase, the optimal dosing frequency is also daily for these patients (strong recommendation, high certainty of evidence) (recommendation 4.3) If a daily continuation phase is not possible for these patients, three times weekly dosing during the continuation phase is an acceptable alternative (conditional recommendation, high or moderate certainty of evidence)	Redundant	**Redundant** **Dosing frequency is daily in all TB treatment regimens.**
WHO's policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. **2012 *(4)***		
(Recommendation B1.3) TB patients with known positive HIV status and TB patients living in HIV-prevalent settings should receive at least 6 months of rifampicin-containing treatment regimen (strong recommendation, high certainty of evidence) The optimal dosing frequency is daily during the intensive and continuation phases (strong recommendation, high certainty of evidence)	Remained valid	**Redundant** **4-month regimens for DS-TB treatment are non-inferior to 6-month regimen in TB patients living with HIV.** **Dosing frequency is daily in all TB treatment regimens.**

(Recommendation 4.4) It is recommended that **TB patients who are living with HIV** should receive at least the same duration of TB treatment as HIV-negative TB patients (strong recommendation, high certainty of evidence)	Remained valid	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2012 guidelines.** Recommendation 8
No recommendation	NEW RECOMMENDATION (recommendation 1.5) In patients with drug-susceptible pulmonary TB who are living with HIV and receiving antiretroviral therapy during TB treatment, a 6-months standard treatment regimen is recommended over an extended treatment for 8 months or longer (conditional recommendation, very low certainty of evidence)	**Redundant** **No recommended treatment regimens for DS-TB treatment exceed 6 months duration.** **4-month regimens for DS-TB treatment are non-inferior to 6-month regimen in TB patients living with HIV.**
Consolidated guidelines on the use of antiretroviral drugs 2016 *(5)*		
HIV antiretroviral medications should be started in all TB patients living with HIV regardless of their CD4 cell count (Strong recommendation, high certainty of evidence)	(Recommendation 1.4.1) ART should be started in all TB patients living with HIV regardless of their CD4 cell count (strong recommendation, high certainty of evidence).	**UPDATED. Recommendation is copied without modification from Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach 2021** **ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 cell count, among people living with HIV.** **Adults and adolescents (strong recommendation, low to moderate certainty of evidence);** **Children and infants (strong recommendation, very low certainty of evidence). (6)** Recommendation 9
TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (Strong recommendation, high certainty of evidence)	(Recommendation 1.4.2) TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (Strong recommendation, high certainty of evidence). HIV-positive patients with profound immunosuppression (e.g. CD4 cell counts less than 50 cells/mm^3) should receive ART within the first 2 weeks of initiating TB treatment.	
HIV-positive TB patients with profound immunosuppression (e.g. CD4 cell counts less than 50 cells/mm^3) should receive ART within the first 2 weeks of initiating TB treatment (based on expert opinion)		

The use of adjuvant steroids in the treatment of TB meningitis and pericarditis		
No recommendation	NEW RECOMMENDATION (Recommendation 1.6.1) In patients with **tuberculous meningitis**, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6–8 weeks should be used (strong recommendation, moderate certainty of evidence)	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2017 guidelines.** **Recommendation 10**
No recommendation	NEW RECOMMENDATION (Recommendation 1.6.2) In patients with **tuberculous pericarditis**, an initial adjuvant corticosteroid therapy may be used (conditional recommendation, very low certainty of evidence)	**Recommendation is copied without modification into this consolidated document and appears exactly as in the 2017 guidelines.** **Recommendation 11**
Tuberculosis care and support		
No recommendation	NEW RECOMMENDATION (Recommendation 2.1.1) Health education about the disease and counselling on treatment adherence should be provided to patients on TB treatment (strong recommendation, moderate certainty of evidence)	**Recommendations are included in the "Tuberculosis Care and support" submodule of the consolidated guidelines**
	NEW RECOMMENDATION (Recommendation 2.1.2) A package of treatment adherence interventions may be offered to patients on TB treatment in conjunction with the selection of a suitable treatment administration option (conditional recommendation, low certainty of evidence)	

	NEW RECOMMENDATION (Recommendation 2.1.3) One or more of the following treatment adherence interventions (complementary and not mutually exclusive) may be offered to patients on TB treatment or to health-care providers: a) tracer or digital medication monitor (conditional recommendation, very low certainty in the evidence) b) material support to patient (conditional recommendation, moderate certainty of evidence); c) psychological support to patient (conditional recommendation, low certainty of evidence); d) staff education (conditional recommendation, low certainty of evidence).

	NEW RECOMMENDATION (recommendation 2.1.4) The following treatment administration options may be offered to patients on TB treatment: a) Community or home-based treatment support is recommended over health facility-based treatment support or unsupervised treatment (conditional recommendation, moderate certainty of evidence); b) Treatment support administered by trained lay providers or health care workers is recommended over treatment support administered by family members or unsupervised treatment (conditional recommendation, very low certainty of evidence); c) Video supported treatment can replace in-person treatment observation when the video communication technology is available, and it can be appropriately organized and operated by health care providers and patients (conditional recommendation, very low certainty of evidence)	
Guidelines for the programmatic management of drug-resistant tuberculosis. **2011** ***(7)***	**Guidelines for treatment of drug-susceptible tuberculosis and patient care 2017** ***(2)***	**WHO consolidated guidelines on tuberculosis Module 4: Treatment** **Drug-susceptible tuberculosis treatment.** **2021**

Patients with MDR-TB should be treated using mainly ambulatory care rather than with models of care based principally on hospitalization (conditional recommendation, very low certainty of evidence)	Remained valid	**Recommendations are part of the consolidated guidelines on DR-TB treatment 2020. These recommendations are consolidated and published in the "Tuberculosis Care and support" submodule of consolidated guidelines.**
No recommendation	NEW RECOMMENDATION (Recommendation 2.2) A decentralized model of care is recommended over a centralized model for patients on MDR-TB treatment (conditional recommendation, very low certainty of evidence)	
TB treatment in children and adolescents		
	Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2014 *(8)*.	
	(Recommendation 8) The following dosages of anti-TB medicines should be used daily for the treatment of TB in children: isoniazid (H) 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day rifampicin (R) 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day pyrazinamide (Z) 35 mg/kg (range 30–40 mg/kg) ethambutol (E) 20 mg/kg (range 15–25 mg/kg) (strong recommendation, moderate certainty of evidence)	**Recommendations that are not redundant and are valid, in addition to all other recommendations relevant to children and adolescents, are featured in the guidelines on childhood TB treatment that are published in the module on management of tuberculosis in children and adolescents of this series of consolidated guidelines.**

	(Recommendation 9) Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence or low prevalence of isoniazid resistance and children who are HIV-negative can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at the dosages specified in Recommendation 8 (strong recommendation, moderate certainty of evidence)	
	(Recommendation 10) Children with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis and/or children with extensive pulmonary disease, living in settings where the prevalence of HIV is high and/or the prevalence of isoniazid resistance is high should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the dosages specified in Recommendation 8 (strong recommendation, moderate certainty of evidence)	

	(Recommendation 11) Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described in recommendation 9 or 10. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing pediatric TB (strong recommendation, low certainty of evidence)
	(Recommendation 12) During the continuation phase of treatment, thrice-weekly regimens can be considered for children known not to be HIV-infected and living in settings with well-established directly observed therapy (conditional recommendation, very low certainty of evidence for use of intermittent treatment of children in specific settings)
	(Recommendation 13) Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculous peripheral lymphadenitis (strong recommendation, moderate certainty of evidence)

	(Recommendation 14) Children with suspected or confirmed tuberculous meningitis and children with suspected or confirmed osteoarticular TB should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months, the total duration of treatment being 12 months. The doses recommended for the treatment of tuberculous meningitis are the same as those described for pulmonary TB (strong recommendation, low certainty of evidence)

References to WHO guidance:

1. Treatment of tuberculosis, guidelines for national programmes, fourth edition. Geneva: World Health Organization; 2010 (https://www.who.int/publications-detail-redirect/9789241547833, accessed 3 March 2022).
2. Guidelines for treatment of drug-susceptible tuberculosis and patient care. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/bitstream/handle/10665/255052/9789241550000-eng.pdf, accessed 3 March 2022).
3. WHO Consolidated guidelines on tuberculosis, Module 4: Treatment – Drug-resistant tuberculosis treatment. Geneva: World Health Organization; 2020 (https://www.who.int/publications-detail-redirect/9789240007048, accessed 3 March 2022).
4. WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva: World Health Organization; 2012 (https://apps.who.int/iris/handle/10665/44789, accessed 3 March 2022).
5. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach, second edition. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/handle/10665/208825, accessed 3 March 2022).
6. Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach. Geneva: World Health Organization; 2021 (https://www.who.int/publications-detail-redirect/9789240031593, accessed 3 March 2022).
7. Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2011 (https://www.who.int/publications-detail-redirect/9789241501583, accessed 3 March 2022).
8. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: World Health Organization; 2014 (https://www.who.int/publications-detail-redirect/9789241548748, accessed 3 March 2022).

Web Annexes

Web Annex 1. Expert panels

Web Annex 2. Declarations of interest

Web Annex 3. PICO questions

Web Annex 4. GRADE evidence profiles and evidence-to-decision tables

Web Annex 5. 2010 and 2017 DS-TB Guidelines

https://apps.who.int/iris/bitstream/handle/10665/353398/9789240048140-eng.pdf

For further information, please contact:

Global Tuberculosis Programme
World Health Organization
20, Avenue Appia CH-1211 Geneva 27 Switzerland
Web site: www.who.int/tb

World Health Organization

9789240048126